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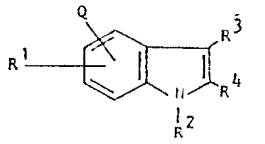
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(54) **Novel acidic indole compounds and their use as antiallergy agents.**

(57) There are disclosed compounds having the following general formula (I):



(I)

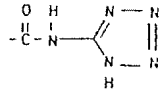
and pharmaceutically acceptable salts thereof, wherein:

R^1 and Q are each, independently, H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, an alkylsulphinyl having from one to four carbon atoms, an alkylsulphonyl having from one to four carbon atoms, a hydroxy group, a nitro group, an amino group, substituted amino group or a halogen, R^1 being further chosen from a methylenedioxy radical attached to adjacent carbon atoms of the benzene ring;

R^2 is H, an alkyl having from one to twelve carbon atoms, a phenyl radical, a substituted phenyl radical or a benzyl radical;

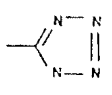
R^3 is H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, a phenylthio radical, a substituted phenylthio radical, an alkylsulphinyl having from one to four carbon atoms, a phenylsulphinyl radical, a substituted phenylsulphinyl radical, an alkylsulphonyl hving from one to four carbon atoms, a phenylsolphonyl radical, a substituted phenylsolphonyl radical an amino group, or a substitued amino group; and

R^4 is



(A)

or



(B)

Methods of preparing the compounds, compositions comprising the compounds and the pharmaceutical use of the compounds are also disclosed.

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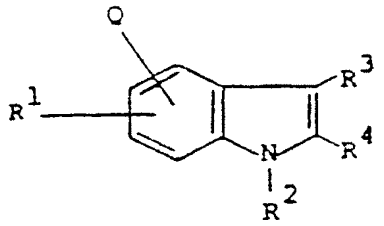
NOVEL ACIDIC INDOLE COMPOUNDS AND THEIR USE AS ANTIALLERGY AGENTS

The present invention provides novel acidic indole compounds, novel methods for synthesis thereof, selected novel intermediates, pharmaceutical compositions and uses of the novel compounds, particularly as antiallergic agents. Additionally, the compounds prevent the release of mediators such as leukotrienes from basophils and neutrophils providing activity useful in cardiovascular disorders as well as in antiinflammatory and antimigraine treatment. See B. Samuelsson, "Leukotrienes: Mediators of Immediate Bypersensitivity Reactions and Inflammation," Science, Vol. 220, pp 568 (1983), P. J. Piper, "Leukotrienes," Trends in Pharmacological Sciences, pp 75 & 77 (1983), and J. L. Romson, et al; "Reduction of the Extent of Ischemic Myocardial Injury by Neutrophil Depletion in the Dog," Circulation, Vol. 67, p 1016 (1983).

European Patent Application 71,935 discloses indole derivatives. However, the novel compounds of the present invention include differences from the compounds in EP 71,935 not suggested by its disclosure.

Furthermore, the antiallergic utility now found for the novel compounds of the present invention is not within the teachings for the indole derivatives disclosed by the EP 71,935 reference.

The present invention is a compound of Formula I,



wherein (1) R^1 and Q are independently H, alkyl of from one to twelve carbons, inclusive, alkoxy of from one to twelve carbons, inclusive, mercapto, alkylthio of from one to four carbons, inclusive, alkylsulfinyl of from one to four carbons, inclusive, alkylsulfonyl of from one to four carbons, inclusive, hydroxy, R^1 taken twice having each on adjacent carbons such that the two R^1s together are methylenedioxy, nitro, amino, substituted amino, or halogen; (2) R^2 is H, alkyl of from one to twelve carbons, inclusive, phenyl, substituted phenyl, or benzyl; (3) R^3 is H, alkyl of from one to twelve carbons, inclusive, alkoxy of from one to twelve carbons, inclusive, mercapto, alkylthio of from one to four carbons, inclusive, phenylthio, substituted phenylthio, alkylsulfinyl of from one to four carbons, inclusive, phenylsulfinyl, substituted phenylsulfinyl, alkylsulfonyl of from one to four carbons, inclusive, phenylsulfonyl, substituted phenyl sulfonyl, amino, and substituted amino; and (4) R^4 is A or B; and pharmaceutically acceptable salts thereof.

Further, the present invention includes a process for the preparation of a compound of Formula I, wherein R^1, Q, R^2, R^3, and R^4 are as defined above, which comprises treating a compound having the Formula III, wherein R^1, Q, R^2, and R^3 are as defined above to obtain the compound of Formula I as shown in Scheme I.

The process which comprises treating the compound of Formula III to obtain the compound of Formula I_1, wherein R^4 of Formula I is the moiety shown by A comprises contacting the compound of Formula III with the compound of Formula II, in the presence of a coupling agent. See Scheme II.

A compound of Formula III is known or can readily be prepared from compounds known in the literature. For example, compounds of Formula III wherein R^3 is an amino or a substituted amino may be prepared in a

manner analogous to or derived from the process described by P. C. Unangst, J. Heterocyclic Chem., Vol. 20, 495 (1983). Unangst describes compounds in which the substituent is an amino. Substituted amino groups can be prepared from the amino compounds by standard methods.

An alternate route to compounds of Formula III having R^3 as amino or substituted amino groups may be analogous to a reaction described by M. A. Khan, et al, in Chem. Pharm. Bull., Vol. 25, 3110 (1977).

Compounds of Formula III wherein R^3 is a mercapto or alkylthio within the present invention is shown or can be made by procedures from analogous compounds to those shown by K. Nagarajan, et al, Indian J. of Chem., Vol. 20B, 672 (1981). Likewise, compounds of Formula III wherein R^3 is alkylsulfinyl or alkylsulfonyl can be prepared by oxidation of the corresponding alkylthio compounds by methods familiar to those skilled in the art.

The process which comprises treating the compound of Formula III to obtain the compound of Formula I_2 wherein R^4 of Formula I is the moiety shown by B is one in which the compound of Formula III is (1) contacted with ammonia and the resulting amide dehydrated to give a compound of Formula IV, wherein R^1, Q, R^2, and R^3 are as defined above and (2) the compound of Formula IV is then treated in a manner analogous to that described by the K. Sisido cited reference hereinafter to give the compound of Formula Formula I_2. See Scheme III.

Additionally, the present invention includes a process for the preparation of the compound of Formula I_3 wherein R^1, Q, and R^2 are as defined above and OR^6 wherein R^6 is benzyl or alkyl of from one to twelve carbons, inclusive, which comprises (1) esterifying a compound of Formula VII, (2) treating the esterification product to obtain a compound of Formula VI

by a reaction analogous to that described by K. Sisido, et al, J. Organometallic Chem., Vol. 33, 337 (1971), protecting the compound of Formula VI wherein Y is an appropriate protecting group, and cyclizing the protected compound, and finally, alkylating with a compound $HalR^6$, wherein R^6 is as defined above, and then deprotecting to obtain the compound I_3. Cyclization is accomplished generally by treating the protected compound of Formula VI with potassium butoxide in tetrahydrofuran. See Scheme IV.

Cyclization can also be used to prepare a compound of Formula IV of Scheme III for use as an intermediate in the preparation of compounds of Formula I_3 described above. For example, esterification of a compound of Formula VIII, wherein R^1 and R^2 are as defined above may be followed by cyclization to obtain the compound IV. See Scheme V.

The antiallergy activity of the compounds having the Formula I of the present invention was determined by the well-known Schultz-Dale procedure, that is described in N. Chand, et al, Agents and Actions, Vol. 8, 171 (1978), or the Herxheimer in vivo antiallergy test, described in H. Herxheimer, J. Physiol. (London) Vol. 117, 251 (1952).

By virtue of this antiallergy activity the compounds of Formula I are useful in treating an allergic hypersensitivity reaction (AHR) having broad symptoms. For example, the symptoms may include dermatitis, lacrimation, nasal discharge, coughing, sneezing, nausea, vomiting, diarrhea, difficulty in breathing, pain, inflammation, and in severe cases, anaphylactic shock, circulatory collapse, and even death. The AHR is found in man as well as other animals suffering from bronchial asthma, seasonal pollinosis (e.g., hayfever), allergic

rhinitis, urticoria, allergic conjunctivitis, food allergies, and anaphylactoid reactions.

In an AHR an antibody (reagin in man) influences the cell membrane of a mast cell by reacting with an antigen, to initiate reactions within the mast cell which ultimately causes release of mediators (bioactive compounds) such as bradykinin, slow reacting substance A (SRS-A), histamine, serotonin (5HT), possibly some prostaglandins, or other not now known substances. The mediator is released from the mast cell whereupon it attaches to suitable receptor sites (e.g., on smooth muscle) resulting in AHR attack symptoms. Various methods are used to relieve the symptoms of AHR. It is not known, however, what mechanism is effected for the antiallergic use by the compounds having Formula I of the present inventions.

Pharmaceutical compositions are prepared from compound Formula I and salts thereof described as the present invention having inert pharmaceutical carriers. The compositions may be either solid or liquid.

A physician or veterinarian of ordinary skill readily determines a subject who is exhibiting AHR symptoms. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically acceptable dosage forms by conventional methods known to the pharmaceutical art.

The compounds can be administered in such oral unit dosage forms such as tablets, capsules, pills, powders, or granules. They also may be administered rectally or vaginally in such forms as suppositories or bougies; they may also be introduced parenterally (e.g., subcutaneously, intravenously, or intramuscularly), using forms known to the pharmaceutical art. They are also introduced directly to an affected area,

(e.g., in the form of eye drops or by inhalation). For the treatment of AHR induced conditions such as erythema, the compounds of the present invention may also be administered topically in the form of ointments, creams, gels, or the like. In general, the preferred route of administration is orally.

An effective but nontoxic quantity of the compound is employed in treatment. The ordinarily skilled physician or veterinarian will readily determine and prescribe the effective amount of the anti-AHR agent to prevent or arrest the progress of the condition. In so proceeding, the physician or veterinarian could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained.

Initial dosages of the compounds of the invention having Formula I are ordinarily in the area of 10 mg up to 2 g per day orally, preferably 10 mg to 500 mg per dose orally, given from one to four times daily or as needed. When other forms of administration are employed equivalent doses are administered.

The compounds of this invention can also be administered as pharmacologically acceptable salts such as can be readily prepared with inorganic and organic bases, such as NaOH, KOH, $Mg(OH_2)$, $Ca(OH)_2$, NH_4OH, substituted ammonium salts, L-arginine, choline, N-methyl glucamine and the like.

The novel compounds of Formula I are named as derivatives of indoles by virtue of a nitrogen containing heterocyclic five-membered ring fused to a phenyl ring. The fused rings are numbered counterclockwise starting with the nitrogen atom at the one position as shown in the ring system of Formula I'.

Certain compounds within the scope of Formula I are preferred, since they have a more advantageous

pharmacologic effect. Preferred compounds include compounds of Formula I wherein Q is hydrogen. Compounds of the Formula I more preferred are the following compounds: (1) 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, and (2) 3-ethoxy-5-methoxy-1-phenyl-N-1H-terazol-5-yl-1H-indole-2carboxamide.

Of the above, the most preferred compound is 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

Alkyl of from one to four carbons, inclusive, is methyl, ethyl, propyl, butyl, or isomeric forms therof.

Alkyl of from one to twelve carbons, inclusive, is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, etc, and includes isomeric forms of the alkyl of from one to six carbons, inclusive. Alkyl of from one to six carbons, inclusive, are preferred.

Alkoxy of from one to twelve carbons, inclusive, is methoxy, ethoxy, propoxy, butoxy, etc, and includes isomeric forms of alkoxy of from one to six carbons, inclusive. Alkoxy of from one to six carbons, inclusive, are preferred.

Substituted phenyl is a phenyl having at least one substiuent and particularly one or two substituents such as, alkyl of from one to four carbons, inclusive, alkoxy of from one to four carbons, inclusive, hydroxy, nitro, amino, substituted amino, mercapto, alkylthio of from one to four carbons, methylenedioxy, or halogen.

Substituted amino is mono- or di-alkyl amino wherein alkyl is from one to four carbons, inclusive.

Halogen is fluoro, chloro, bromo, iodo, or trifluoromethyl.

The compounds of this invention are synthesized as illustrated in Schemes I-V.

Generally, the compounds having the Formula I, as illustrated in Scheme I are prepared by treating an

indole-2-carboxylic acid of Formula III wherein R^1, Q, R^2, and R^3 are as defined above.

A 3-alkoxy ester of Formula IX, wherein R^1, Q, and R^2 are as defined above, R^3 is alkoxy, and R^5 is benzyl or alkyl of from one to six, inclusive, as shown in Scheme VI may be prepared by methods analogous to those known in the literature. See for example, H. Plieninger, et al, Chem. Ber., Vol. 104, 1863 (1971), and J. Galun, et al, J. Heterocyclic Chem., Vol. 16, 221 (1979). If R^3 is hydroxy in the compound of Formula IX it must be protected by, for example, treatment with a compound of Formula R^6X wherein R^6 is alkyl of from one to six carbons, inclusive, or benzyl and X is halogen, sulfonate or the like using conditions analogous to those known in the art. Protection of other R^1, Q, R^2, or R^3 groups is also readily understood by those skilled in the art.

The 3-alkoxy ester is then converted to carboxylic acids of Formula III wherein R^1, Q, and R^2, are as defined above, and R^3 is alkoxy.

The conversion is accomplished using standard conditions, such as, using either a strong base, NaOH, KOH, and the like, or analogous organic bases such as, potassium tertiary-butoxide, or the like followed by acidification. (see a similar process in indole chemistry in the A. Galun, et al, reference cited above).

Additionally, the general preparation of a compound of Formula I wherein R^4 is A, R^3 is amino or substituted amino and R^1, Q, and R^2 are as defined above may also be accomplished as shown in Scheme VII. That is, a mixture of a compound of Formula XX wherein R^1, Q, and R^2 are as defined above and an alkylaldehyde of from one to four carbons, inclusive in a solvent such as tetrahydrofuran, acetonitrile or the like, is treated

with sodium cyanoborohydride. The resulting compound of Formula XXI wherein R^7 and R^8 are independently hydrogen or alkyl of from one to four carbons, inclusive, and R^1 and Q are as defined above is then reacted with R^2 Cl or R^2 Br wherein R^2 is as defined above to obtain the compound of Formula IX. Such a compound of Formula IX, wherein R^1, Q, R^2 and R^7 and R^8 are as defined above may be directly coupled with the compound of Formula II in the presence of lithium diisopropylamine or treated as shown in Schemes VI and further, optionally treated as for Schemes I, II or III as described above.

A compound of Formula XX wherein R^1 is 5-methoxy and Q is hydrogen is known and is prepared by the procedure described in S. V. Simakov, et al, Khim-Farm. Zh., 17, p. 1183 (1983). Other definitions for R^1 and Q in the compound of Formula XX may be prepared by analogues procedures.

The preparation of XXI is generally conducted by the procedures known as reductive amination and the further reaction to convert the compound of Formula XXI to the compound of Formula IX_1, is analogous to the reaction having conditions known as an Ullmann reaction.

Also, the compound of Formula I wherein R^4 is A, and R^3 is alkylthio or alkylsulfonyl may be prepared by the processes shown in Scheme VIII. The compounds of Formula XXX wherein R^1 and Q are as defined above are prepared by known methods, methods analogous to known methods or are commercially available and are reacted with R^2 Br or R^2Cl wherein R^2 is as defined above using conditions analogous to those described as an Ullmann reaction and shown as step 2 of Scheme VIII. Then the carboxylic acid group is protected, for example, by reaction with CH_3I to form an ester of Formula XXXII wherein R^1, Q, and R^2 are as defined above and then treated with thionyl

chloride in a reaction similar to that described by J. Szmuszkovicz, J. Org. Chem., 29, p 178 (1964) to obtain the sulfinyl chloride of Formula XXXIII wherein R^1, Q, and R^2 are as defined above.

The compound of Formula XXXIII reacts with a Grignard reagent or an alkyl cuprate reagent to yield alkylsulfinyl or phenyl- or substituted phenyl-sulfinylindoles of the Formula XXXIV wherein R^9 is alkyl of from one to four carbons, inclusive, phenyl or substituted phenyl. The sulfinyl indoles of Formula XXXIV may then be reduced with trifluoroacetic anhydride and sodium iodide to provide the compound of Formula IX, or further reacted to give the compound of Formula IX_3. Again the Formula IX may be coupled with 5-aminotetrazol by various procedures discussed above to give a compound of Formula I wherein R^3 is SR^9 wherein R^9 is as defined above and R^1, Q, and R^2 are also as defined above. A compound of Formula I wherein R^3 is SR^9 may of course, be further treated with standard oxidizing reagents such as potassium permanganate, metachloroperbenzoic acid, or the like using conditions analogous to those known for similar reactions to obtain a compound of Formula I^4 wherein R^9 is as defined above. The preparation of compounds of Formula I wherein R^3 is a sulfur containing group as described hereinabove is shown in Scheme VIII.

Particularly, the processes described above include compounds wherein R^1 is 5-methoxy, Q is hydrogen, and R^2 is phenyl or benzyl beginning with either a commercially available compound or a compound described by Y. Murakami, et al. in Synthesis p 738 (1984).

The 3-alkoxy carboxylic acids of Formula III may be purified by conventional methods or employed without separation in the step shown in Scheme I.

This step is accomplished by methods known in the art, for example, by coupling the 3-alkoxy carboxylic acids of Formula III with 5-aminotetrazole of Formula II, in the presence of coupling agents. Such agents include 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide, and the like. See Scheme II. Appropriate solvents for the step shown in Scheme II may be, for example, N,N-dimethylforamide (DMF), acetonitrile, tetrahydrofuran, chloroform, or dichloromethane. Recrystallization of compounds I, may be accomplished in various solvents, such as N,N-dimethylformamide (DMF) either alone or in combination with H_2O, acetonitrile in combination with water or with DMF and water, acetone, ethyl acetate, methanol alone or in combination with water, 2-methoxyethanol in combination with water, 2-propanol either in combination with water or in combination with DMF and water.

The starting materials required for the processes described in this invention are either commercially available or they can be synthesized by methods known in the art of organic chemistry. For example, an acid intermediate having the Formula III wherein R^1, Q, and R^2 are hydrogen, R^3 is methoxy, is described by N. T. Modi, et al, J. Org. Chem., Vol. 35, 2228 (1970), and a methyl ester of the compound having the Formula III, wherein R^1 and Q are hydrogen, R^2 is methyl, is as described in French Patent Number 1,503,908 (see Chem. Abst., Vol. 70, 37, 651 (1969). Likewise, an ester of the acid having the Formula III, wherein R^1 is methoxy or chloro, Q is hydrogen, R^2 is phenyl or 4-methoxyphenyl, R^3 is hydroxy, can be prepared in a manner analogous to that described by P. Friedlander, et al, Chem. Ber., Vol. 55, 1597 (1922). Also, various esters of acids of indole compounds for use as precursors in a process of the present invention can be made in view of the teachings of

P. C. Unangst, et al, J. Heterocyclic Chem., Vol. 21, 709 (1984).

Under certain circumstances it is necessary to protect either the N or O of intermediates in the above noted process with suitable protecting groups which are known. Introduction and removal of such suitable oxygen and nitrogen protecting groups are well known in the art of organic chemistry; see for example, (1) "Protective Groups in Organic Chemistry," J. F. W. McOmie, ed., (New York, 1973), pages 43ff, 95ff; (2) J. F. W. McOmie, Advances in Organic Chemistry, Vol. 3, 191-281 (1963); (3) R. A. Borssonas, Advances in Organic Chemistry, Vol. 3, 159-190 (1963); and (4) J. F. W. McOmie, Chem. & Ind., 603 (1979).

Examples of suitable oxygen protecting groups are benzyl, t-butyldimethylsilyl, ethoxyethyl, and the like. Protection of an N-H containing moiety is necessary for some of the processes described herein for the preparation of compounds of this invention. Suitable nitrogen protecting groups are benzyl, triphenylmethyl, trialkylsilyl, trichloroethylcarbamate, trichloroethoxycarbonyl, vinyloxycarbamate, and the like.

Under certain circumstances it is necessary to protect two different oxygens with dissimilar protecting groups such that one can be selectively removed while leaving the other in place. The benzyl and t-butyldimethylsilyl groups are used in this way; either is removable in the presence of the other, benzyl being removed by catalytic hydrogenolysis, and t-butyldimethylsilyl being removed by reaction with, for example, tetra-n-butylammonium fluoride.

In the process described herein for the preparation of compounds of this invention the requirements for protective groups are generally well recognized by one skilled in the art of organic chemistry, and accordingly the use of appropriate protecting groups

is necessarily implied by the processes of the charts herein, although not expressly illustrated.

The products of the reactions described herein are isolated by conventional means such as extraction, distillation, chromatography, and the like.

The salts of compounds of Formula I described above are prepared by reacting the appropriate base with a stoichometric equivalent of the acid indole compounds of Formula I to obtain pharmacologically acceptable salts thereof.

The compounds of this invention may also exist in hydrated or solvated forms.

The process of this invention is further elaborated by the representative examples as follows.

EXAMPLE 1

3-Methoxy-1-(phenylmethyl)-1H-indole-2-carboxylic acid

A mixture of 4.6 g (0.096 mole) of 50% sodium hydride/mineral oil in 100 ml of N,N-dimethylformamide under a nitrogen atmosphere was cooled in an ice bath. To the stirred mixture was added over 45 minutes, a solution of 19.5 g (0.089 mole) of 3-methoxy-1H-indole-2-carboxylic acid ethyl ester [A. Galun, A. Markus, and A. Kampf, J. Heterocyclic Chem., 16, 221 (1979)] in 50 ml of N,N-dimethylformamide. The mixture was stirred for an additional 30 minutes, and a solution of 11.6 ml (16.7 g; 0.098 mole) of benzyl bromide in 10 ml of N,N-dimethylformamide was added over 15 minutes. The ice bath was removed, the mixture was stirred for an additional 16 hours, and then added to 800 g of ice water. The crude ester intermediate

was removed by extracting with dichloromethane (4 x 250 ml). The combined organic layers were back-washed with brine (3 x 500 ml), dried (anhydrous sodium sulfate), and evaporated to yield a crude residue of 3-methoxy-1(phenylmethyl)-1H-indole-2-carboxylic acid ethyl ester, plus a small amount of N,N-dimethylformamide.

The total crude residue described above was dissolved in 180 ml of methanol and treated with a solution of 14.2 g (0.25 mole) of potassium hydroxide in 180 ml of water. The mixture was stirred at reflux for three hours, cooled, condensed to approximately one-third its original volume (rotary evaporator), and partitioned between 750 ml of water and 300 ml of dichloromethane. The aqueous layer was separated, washed with fresh dichloromethane (2 x 300 ml), filtered, and cooled in ice. Acidification with 4.0 N hydrochloric acid yielded the crude carboxylic acid product. The product was filtered and washed with water to yield 17.1 g (68% yield) of final product. A sample recrystallized from ethyl acetate/hexane was analytically pure, mp 115-117°C.

EXAMPLE 2

1-Hexyl-3-methoxy-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 1 from 27.0 g (0.12 mole) of 3-methoxy-1H-indole-2-carboxylic acid ethyl ester [A. Galun, A. Markus, and A. Kampf, J. Heterocyclic Chem., 16, 221 (1979)] alkylated with 22.1 g (0.13 mole) of 1-bromohexane.

Saponification of 20.7 g (0.068 mole) of the crude intermediate 1-hexyl-3-methoxy-1H-indole-2-carboxylic acid ethyl ester as described in Example 1 yielded 14.1 g (75% yield) of the crude carboxylic acid product. A sample recrystallized several times from hexane was analytically pure, mp 65-67°C.

EXAMPLE 3

3,5-Dimethoxy-1-phenyl-1H-indole-2-carboxylic acid

A mixture of 10.8 g (0.036 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)] and 5.5 g (0.040 mole) of anhydrous potassium carbonate in 100 ml of acetone was treated with 3.7 ml (4.9 g; 0.039 mole) of dimethyl sulfate. The mixture was stirred and heated at reflux for 16 hours, cooled, and filtered. The filter cake was washed several times with fresh acetone, and the combined filtrates were evaporated (vacuum) to yield a crude residue of 3,5-dimethoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester.

The total crude residue described above was saponified with 6.3 g (0.11 mole) of potassium hydroxide by the procedure described in Example 1. There was obtained 9.8 g (91% yield) of crude carboxylic acid. Recrystallization from aqueous acetone yielded the carboxylic acid product in analytical purity, mp 150°C-dec.

EXAMPLE 4

3-Methoxy-1-phenyl-1H-indole-2-carboxylic acid

A suspension of 3.9 g (0.081 mole) of 50% sodium hydride/mineral oil in 85 ml of N,N-dimethylformamide under a nitrogen atmosphere was cooled in ice and treated portionwise over 90 minutes with 17.1 g (0.064 mole) of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. Friedlander and K. Kunz, Chem. Ber., 55, 1597 (1922)]. The mixture was stirred in ice an additional one hour, 7.9 ml (10.5 g; 0.083 mole) of dimethyl sulfate was added dropwise over 15 minutes, the ice bath was removed,

and stirring was continued for a total of 65 hours. The reaction mixture was added to 600 g of ice/water, acidified with 4.0 N hydrochloric acid, and extracted with dichloromethane (4 x 250 ml). The combined organic layers were washed with water (3 x 500 ml), dried (anhydrous sodium sulfate), and evaporated to yield a crude residue of 3-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester, plus a small amount of N,N-dimethylformamide.

The total crude residue described above was saponified with 11.4 g (0.20 mole) of potassium hydroxide by the procedure described in Example 1. There was obtained 14.4 g (84% yield) of crude carboxylic acid product. A sample recrystallized from ethyl acetate/hexane was analytically pure, mp 115°C-dec.

EXAMPLE 5

1-Phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid methyl ester

A mixture of 1.2 g (0.025 mole) of 50% sodium hydride/mineral oil suspension in 20 ml of hexamethylphosphoramide under a nitrogen atmosphere was cooled in ice and treated over 15 minutes with a solution of 5.3 g (0.020 mole) of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. Friedlander and K. Kurz, Chem. Ber., 55, 1597 (1922)] in 25 ml of hexamethylphosphoramide. The mixture was stirred in ice an additional one hour, 2.6 ml (2.9 g, 0.023 mole) of benzyl chloride was added in one portion, the ice bath was removed and stirring was continued for a total of 18 hours. The reaction mixture was added to 200 g of ice/water, stirred for one hour, and the precipitated product was filtered and washed with water. Recrystallization from aqueous

methanol yielded 3.8 g (54% yield) of the ester product. An additional recrystallization as above yielded analytically pure ester, mp 117-119°C.

EXAMPLE 6

1-Phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid

A mixture of 11.9 g (0.033 mole) of the ester described in Example 5 in 200 ml of dimethyl sulfoxide under a nitrogen atmosphere was treated with 7.4 g (0.066 mole) of potassium tert-butoxide. The mixture was stirred and heated to 65°C for two hours, cooled, and added to 2.5 kg ice/water. The aqueous mixture was filtered, and the filtrate was cooled in ice and acidified with 6.0 N hydrochloric acid to precipitate the crude carboxylic acid product. The product was filtered and washed with water to yield 9.7 g (89% yield) of final product. A sample recrystallized from ethyl acetate/hexane was analytically pure, mp 140-142°C.

EXAMPLE 7

5-Methoxy-1-phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid

A mixture of 155 g (0.52 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)], 83.0 g (0.60 mole) of anhydrous potassium carbonate, and 68 ml (97.8 g; 0.57 mole) of benzyl bromide in 2250 ml of acetone was stirred at reflux for 20 hours. The mixture was cooled, filtered, and the filter cake was washed several times with fresh acetone. The combined filtrates were evaporated (vacuum) to yield a crude

residue of 5-methoxy-1-phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid methyl ester.

The total crude residue described above was dissolved in 1.0 l of methanol. The solution was treated with a solution of 83 g (1.48 mole) of potassium hydroxide in 1.0 l of water, and the new mixture was stirred at reflux for three hours. The reaction mixture was cooled, filtered, and the filtrate was added to 7.0 kg of ice/water. The aqueous solution was cooled in ice and acidified with glacial acetic acid to precipitate the crude carboxylic acid product. The product was filtered and washed with water to yield 174 g (89% yield) of final product. A sample recrystallized from aqueous acetone was analytically pure, mp 123°C-dec.

EXAMPLE 8

5-Methoxy-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid

A stirred mixture of 24.8 g (0.22 mole) of potassium tert-butoxide in 100 ml of dimethyl sulfoxide (under a nitrogen atmosphere) was placed in a cold water bath. A solution of 44.6 g (0.15 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)] in 100 ml of dimethyl sulfoxide was added over 30 minutes. The new mixture was stirred for an additional 45 minutes, and 25.0 ml (32.8 g, 0.27 mole) of 2-bromopropane was added in one portion. The cooling bath was removed, and the mixture was stirred at room temperature for 45 hours, then added to 2.5 kg ice water. The crude ester intermediate was removed by extracting with dichloromethane (4 x 800 ml). The combined organic layers were washed with water (1 x 2.0 l),

5% aqueous sodium bicarbonate (2 x 2.0 l), and water again (1 x 2.0 l), before being dried with anhydrous sodium sulfate. Evaporation (vacuum) yielded a crude residue of 5-methoxy-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester.

The total crude residue described above was dissolved in 300 ml of methanol and the solution was treated with a solution of 22.5 g (0.40 mole) of potassium hydroxide in 300 ml of water. The mixture was stirred at reflux for three hours, cooled, and condensed on a rotary evaporator until a precipitate began to form. After standing for several hours, the precipitated carboxylic acid potassium salt was filtered and washed with cold acetone. The solid was dissolved in 850 ml of water plus 140 ml of acetone by warming slightly. The new solution was cooled in ice and treated with 10 ml of glacial acetic acid to precipitate the crude product. The solid was filtered and washed with water to yield 33.4 g (68% yield) of the carboxylic acid product. A sample recrystallized from aqueous methanol was analytically pure, mp 110°C-dec.

EXAMPLE 9

3-Ethoxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 8 from 30.0 g (0.10 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester alkylated with 67.5 ml (79.4 g; 0.51 mole) of diethyl sulfate.

The crude 3-ethoxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 1 to yield 27.5 g (88% yield) of the crude carboxylic acid product. A sample recrystallized several times from aqueous methanol was analytically pure, mp 130°C-dec.

EXAMPLE 10

3-Hydroxy-1-(4-methoxyphenyl)-1H-indole-2-carboxylic acid methyl ester

Prepared in a manner analogous to the multi-step procedure described [P. Friedlander and K. Kunz, Chem. Ber., 55, 1597 (1922)] for the preparation of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester, with 2-(4-methoxyphenylamino)benzoic acid substituted for 2-(phenylamino)benzoic acid in the first step of the synthetic sequence. The final indole product was recrystallized from 2-propanol to yield analytically pure product, mp 153-155°C.

EXAMPLE 11

1-(4-Methoxyphenyl)-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester

Prepared by the procedure described in Example 8 from 5.0 g (0.017 mole) of 3-hydroxy-1-(4-methoxyphenyl)-1H-indole-2-carboxylic acid methyl ester alkylated with 3.6 ml (4.7 g; 0.038 mole) of 2-bromopropane. After addition of the total reaction mixture to water, the precipitate was filtered and washed with water to yield 5.6 g (95% yield) of crude ester product. A sample recrystallized from methanol was analytically pure, mp 129-131°C.

EXAMPLE 12

1-(4-Methoxyphenyl)-3-(1-methylethoxy)-1H-indole-2-carboxylic acid

Prepared by the saponification procedure described in Example 7 from 5.0 g (0.015 mole) of 1-(4-methoxyphenyl)-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester and 12.0 g (0.20 mole)

of potassium hydroxide. The crude product was recrystallized from ether/hexane to yield 3.8 g (78% yield) of analytically pure carboxylic acid product, mp 129°C-dec.

EXAMPLE 13

5-Chloro-3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester

Prepared in a manner analogous to the multi-step procedure described [P. Friedlander and K. Kunz, Chem. Ber., 55, 1597 (1922)] for the preparation of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester, with 5-chloro-2-(phenylamino)benzoic acid substituted for 2-(phenylamino)benzoic acid in the first step of the synthetic sequence. The final indole product was recrystallized from aqueous 2-methoxy-ethanol to yield analytically pure product, mp 170-173°C.

EXAMPLE 14

5-Chloro-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 8 from 13.9 g (0.046 mole) of 5-chloro-3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester alkylated with 7.7 ml (10.1 g; 0.082 mole) of 2-bromopropane.

The crude 5-chloro-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate (14.8 g; 0.043 mole) was saponified with 6.4 g (0.11 mole) of potassium hydroxide as described in Example 1 to yield 10.2 g (72% yield) of the crude carboxylic acid product, mp 120°-dec. This material was used for further synthesis without additional purification.

EXAMPLE 15

3-Methoxy-1-nonyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 1 from 20.0 g (0.091 mole) of 3-methoxy-1H-indole-2-carboxylic acid ethyl ester [A. Galun, A. Markus, and A. Kampf, J. Heterocyclic Chem., 16, 221 (1979)], alkylated with 19 ml (20.6 g; 0.099 mole) of n-nonyl bromide.

The crude 3-methoxy-1-nonyl-1H-indole-2-carboxylic acid ethyl ester intermediate was saponified as described in Example 1 to yield 18.0 g (62% yield) of the crude carboxylic acid product. This material was used for further synthesis without additional purification.

EXAMPLE 16

3-(1-Methylethoxy)-1-phenyl-1H-indole-2-carboxylc acid

Prepared by the procedure described in Example 8 from 9.5 g (0.036 mole) of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. Friedlander and K. Kunz; Chem. Ber., 55, 1597 (1922)], alkylated with 5.9 ml (7.7 g; 0.063 mole) of 2-bromopropane.

The crude 3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 1 to yield 8.3 g (79% yield) of the crude carboxylic acid product, mp 100°-dec. This material was used for further synthesis without additional purification.

EXAMPLE 17

5-Methoxy-3-(n-nonyloxy)-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 7 from 20.0 g (0.067 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)], alkylated with 14 ml (15.2 g; 0.073 mole) of n-nonyl bromide.

A 1.0 g (0.0024 mole) sample of the crude 5-methoxy-3-(n-nonyloxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 6 (except that the saponification was carried out at 25°C for 18 hours) to yield 0.35 g (36% yield) of the crude carboxylic acid product, mp 81-84°C. This material was used for further synthesis without additional purification.

EXAMPLE 18

3-(n-Dodecyloxy)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 8 from 10.0 g (0.034 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)], alkylated with 12.6 g (0.037 mole) of n-dodecyl p-toluene-sulfonate [C. S. Marvel and V. C. Sekera, Organic Syntheses Coll. Vol. 3, p. 366].

A 1.0 g (0.0022 mole) sample of the crude 3-(n-dodecyloxy)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 6 (except that the reaction was carried out at 25°C for 21 hours) to

yield 0.38 g (39% yield) of the crude carboxylic acid product, mp 85-87°C. This material was used for further synthesis without additional purification.

EXAMPLE 19

2-[(Carboxymethyl)methylamino]-5-methoxybenzoic acid

A mixture of 244 g (0.91 mole) of the potassium salt of 2-bromo-5-methoxybenzoic acid (prepared by treating a solution of the parent carboxylic acid in 2-propanol with excess methanolic potassium hydroxide), 196 g (1.54 mole) of the potassium salt of N-methylglycine (prepared as above), 13 g (0.82 mole) of anhydrous potassium carbonate and 0.66 g (0.01 mole) of copper powder in 220 ml of water was stirred at reflux for five hours. The mixture was cooled, added to 4.0 kg of ice/water, and acidified with concentrated hydrochloric acid to precipitate the crude product. THe solid was filtered and washed with water to yield 186 g (86% yield) of the carboxylic acid product. A sample recrystallized from aqueous 2-methoxyethanol was analytically pure, mp 196°C-dec.

EXAMPLE 20

2-[(Carboxymethyl)methylamino]-5-methoxybenzoic acid dimethyl ester

A mixture of 186 g (0.78 mole) of 2-[(carboxymethyl)methylamino]-5-methoxybenzoic acid in 1.0 l of N,N-dimethylformamide was stirred and treated with a 25% aqueous solution of sodium hydroxide (62.2 g; 1.56 mole). The mixture was stirred for an additional 20 minutes, and 139 ml (316 g; 2.22 mole) of iodomethane was added in one portion. After stirring for 16 hours, the mixture was added to 4.0 kg of ice/water, and the ester product was removed by

extracting with dichloromethane (4 x 1.5 l). The combined organic layers were washed with water (1 x 2.0 l), saturated aqueous sodium bicarbonate (3 x 2.0 l), and water again, dried (anhydrous sodium sulfate), and evaporated. The crude diester residue (containing some residual N,N-dimethylformamide) was cyclized to the corresponding indole without additional purification.

EXAMPLE 21

3-Hydroxy-5-methoxy-1-methyl-1H-indole-2-carboxylic acid methyl ester

The total crude diester residue described in Example 20 was dissolved in 1.0 l of methanol under a nitrogen atmosphere. To the stirred mixture was added 54.6 g (1.01 mole) of sodium methoxide in one portion. The mixture was stirred at reflux for three hours, cooled, added to 4.0 kg of ice/water, and acidified with glacial acetic acid to precipitate the product. The solid was filtered and washed with water to yield 71.7 g (39% yield) of the indole product. A sample recrystallized from aqueous methanol was analytically pure, containing 0.25 mole of water of hydration, mp 103-105°C.

EXAMPLE 22

5-Methoxy-1-methyl-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester

Prepared by the procedure described in Example 8 from 69.6 g (0.30 mole) of 3-hydroxy-5-methoxy-1-methyl-1H-indole-2-carboxylic acid methyl ester alkylated with 27.8 ml (36.3 g; 0.30 mole) of 2-bromopropane. After addition of the total reaction mixture to water, the precipitate was

filtered and washed with water to yield 45 g (55% yield) of crude ester product. A sample recrystallized from aqueous methanol was analytically pure, mp 87-89°C.

EXAMPLE 23

5-Methoxy-1-methyl-3-(1-methylethoxy)-1H-indole-2-carboxylic acid

Prepared by the saponification procedure described in Example 7 from 41.2 g (0.15 mole) of 5-methoxy-1-methyl-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester and 16.7 g (0.30 mole) of potassium hydroxide. The crude acid product was 18.3 g (47% yield). A sample recrystallized from aqueous 2-methoxyethanol was analytically pure, mp 110-112°C.

EXAMPLE 24 (PROCEDURE A)

3-Methoxy-1-(phenylmethyl)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

A mixture of 3.0 g (0.011 mole) of 3-methoxy-1-(phenylmethyl)-1H-indole-2-carboxylic acid and 3.7 g (0.023 mole) of 1,1'-carbonyldiimidazole in 15 ml of N,N-dimethylformamide was stirred and heated on the steam bath under a nitrogen atmosphere for 20 minutes. The mixture was cooled, 1.3 g (0.013 mole) of 5-aminotetrazole monohydrate was added, and heating was continued for an additional 20 minutes. The cooled reaction mixture was added to 150 g of ice/water. Acidification with 4.0 N hydrochloric acid yielded the carbamoyltetrazole product. The crude product was filtered, washed with water, and recrystallized from 2-methoxyethanol/water to yield analytically pure product. There was obtained 2.3 g (63% yield) of product, mp 230°C-dec.

EXAMPLE 25 (PROCEDURE B)

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

A mixture of 20.0 g (0.062 mole) of 5-methoxy-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid and 11.3 g (0.070 mole) of 1,1'-carbonyldiimidazole in 375 ml of acetonitrile was stirred at reflux (under a nitrogen atmosphere) for 90 minutes. The mixture was cooled, and 6.2 g (0.073 mole) of anhydrous 5-aminotetrazole was added, followed by 20.6 ml (15 g; 0.15 mole) of triethylamine. After stirring at reflux for an additional 16 hours, the mixture was cooled, added to 1.5 kg of ice/water and acidified with glacial acetic acid. The precipitated product was filtered and washed with water. Recrystallization from aqueous acetonitrile yielded 19.0 g (79% yield) of analytically pure carbamoyltetrazole product, mp 227°C-dec.

Additionally the following compounds of Formula I may be prepared by methods analogous to Procedures A or B above:

3-Methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 235°C-dec.

3-Methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 240°C-dec.

1-Hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 210°C-dec.

3-Methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 199-200°C.

3-Methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 215°C-dec.

1-Phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 208°C-dec.

3-(1-Methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 203-205°C.

1-(4-Methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 166°C-dec.

5-Chloro-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 228°C-dec.

5-Methoxy-1-methyl-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxyamide, mp 222-225°C.

3,5-Dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 220°C-dec.

3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 226°C-dec.

5-Methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 212°C-dec.

5-Methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 203-204°C.

3-(n-Dodecyloxy)5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 185-186°C.

EXAMPLE 26

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide L-arginate salt

A suspension of 2.76 g (0.007 mole) of 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide in 40 ml of methanol was warmed on a steam bath and treated with a solution of 1.22 g (0.007 mole) of L-arginine dissolved in a minimum of hot water. The mixture was digested until nearly one phase and filtered hot. Cooling to room temperature resulted in precipitation of the arginine salt product. The solid was filtered and washed several times with cold acetone to yield 2.77 g (70% yield) of analytically pure arginine salt, containing 0.50 mole of water of hydration, mp 218°C-dec.

EXAMPLE 27

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1 -tetrazol-5-yl-1H-indole-2-carboxamide sodium salt

A suspension of 7.85 g (0.020 mole) of 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide in 175 ml of methanol was warmed on the steam bath and treated with 10.0 ml of 2.0 N aqueous sodium hydroxide solution. The mixture was digested for a few minutes, filtered hot, cooled, and evaporated. The residue was redissolved and reevaporated several times in 50% acetone/methanol. There was obtained 7.5 g (90% yield) of the amorphous sodium salt product, analytically pure containing 1.0 equivalent of water of hydration, mp 205°C-dec.

EXAMPLE 28

3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide L-arginate salt

Prepared by the procedure described in Example 26 from 2.8 g (0.0074 mole) of 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide and 1.3 g (0.0075 mole) of L-arginine, except that the solvent was ethanol rather than methanol. There was obtained 2.6 g (63% yield) of the arginine salt product, analytically pure containing 1.0 equivalent of water of hydration, mp 165°C-dec.

EXAMPLE 29

3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide sodium salt

Prepared by the procedure described in Example 27 from 7.57 g (0.020 mole) of 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, and

10.0 ml of 2.0 N aqueous sodium hydroxide solution. There was obtained 7.27 g (91% yield) of the amorphous sodium salt product, analytically pure containing 0.50 equivalent of water of hydration, mp 195°C-dec.

EXAMPLE 30

2-[(Cyanomethyl)phenylamino]-5-methoxybenzoic acid methyl ester

A mixture of 7.1 g (0.025 mole) of 2-[(cyanomethyl)phenylamino]-5-methoxybenzoic acid [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1974)], 4.0 g (0.029 mole) of anhydrous potassium carbonate, and 3.0 ml (4.0 g; 0.032 mole) of dimethyl sulfate in 200 ml of acetonitrile was stirred at reflux for 24 hours. The mixture was cooled and filtered, and the filter cake was washed several times with fresh acetonitrile. The combined filtrates were evaporated to an oil, which crystallized upon standing at room temperature. Recrystallization from aqueous methanol yielded 5.1 g (68% yield) of the ester product. A sample recrystallized again as above was analytically pure, mp 107-109°C.

EXAMPLE 31

3-Hydroxy-5-methoxy-1-phenyl-1H-indole-2-carbonitrile

A mixture of 8.4 g (0.075 mole) of potassium tert.-butoxide in 200 ml of tetrahydrofuran (under a nitrogen atmosphere) was stirred and cooled in an ice bath. A solution of 13.7 g (0.046 mole) of 2-[(cyanomethyl)phenylamino]-5-methoxybenzoic acid methyl ester in 150 ml of tetrahydrofuran was added over two hours, the ice bath was removed, and the new mixture was stirred for an additional 42 hours. The

total reaction mixture was added to 1.1 kg of ice/water and acidified with 12.0 ml of glacial acetic acid to precipitate the crude product. The solid was filtered, washed with water, and recrystallized from aqueous methanol to yield 10.3 g (84% yield) of the nitrile product. A sample recrystallized again as above was analytically pure, mp 182°C-dec.

EXAMPLE 32

3-Ethoxy-5-methoxy-1-phenyl-1H-indole-2-carbonitrile

Prepared by the procedure described in Example 8 from 2.2 g (0.0083 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carbonitrile alkylated with 3.3 ml (3.9 g; 0.025 mole) of diethyl sulfate. The crude product was recrystallized from aqueous propanol to yield 1.6 g (67% yield) of the alkylated nitrile product. An additional recrystallization as above yielded an analytically pure sample, mp 97-99°C.

EXAMPLE 33

3-(Diethylamino)-5-methoxy-1H-indole -2-carboxylic acid, ethyl ester

A stirred solution of 12.0 g (0.051 mole) of 3-amino-5-methoxy-1H-indole-2-carboxylic acid, ethyl ester (S. V. Simakov, et al, Khim-Farm Zh., 17, 1183 (1983) and 11.5 g (0.26 mole) of acetaldehyde in 250 ml of acetonitrile (under a nitrogen atmosphere) was cautiously treated with 14.0 g (0.22 mole) of sodium cyanoborchydride. After stirring for 15 minutes, 4.0 ml (4.2g; 0.07 mole) of acetic acid was added in portions over two hours. The reaction mixture was poured over a mixture of ice and 400 ml of 1.0 N sodium hydroxide solution, and the new mixture was extracted with ether. The combined ether layers were

washed several times with brine, dried (anhydrous magnesium sulfate), and evaporated to an orange oil. Flash chromatographic purification (silica gel, methylene chloride/ethyl acetate/hexane (1:6:3) elution) of the residual oil yielded 11.5 g (76% yield) of the analytically pure ester product, mp 85-89°C.

EXAMPLE 34

3-(Diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

A mixture of 3.0 g (0.010 mole) of 3-(diethylamino)-5-methoxy-1H-indole-2-carboxylic acid, ethyl ester, 5.0 g (0.036 mole) of potassium carbonate, 0.50 g (0.009 mole) of potassium hydroxide, 0.30 g (0.001 mole) of copper(I)bromide, and 30.0 ml (44.7 g; 0.28 mole) of bromobenzene under an argon atmosphere was stirred and heated at reflux for three hours. The reaction mixture was filtered while hot through a bed of Celite filter-aid. The filter cake was washed twice with warm toluene, and the combined filtrates were evaporated. The residue was dissolved in a small amount of dichloromethane and purified by flash chromatography (silica gel, 15% ethyl acetate in hexane elution) to yield 2.4 g (66% yield) of intermediate, 3-(diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, ethyl ester, as an oil.

A solution of 2.0 ml (1.44 g; 0.014 mole) of diisopropylamine in 20 ml of tetrahydrofuran under a nitrogen atmosphere was cooled to -10°C and treated with 5.4 ml (0.014 mole) of 2.6 M n-butyllithium in hexane. After stirring for five minutes, a solution of 0.43 g (0.0051 mole) of anhydrous 5-aminotetrazole in 20 ml of 1,3-dimethyl-2-imidazolidinone was added dropwise. The reaction

mixture was stirred for two hours at -10°C, and then a solution of 1.7g (0.0046 mole) of the previously described 3-(diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, ethyl ester in 20 ml of tetrahydrofuran was added dropwise. The new mixture was stirred for three hours at -10°C, then quenched by the addition of aqueous saturated ammonium chloride solution. The total reaction mixture was added to 100 ml of ice water and extracted twice with ether (organic layers discarded). The aqueous phase was cooled in ice and acidified to pH 4 with dilute hydrochloric acid to precipitate 0.25 g (13% yield) of the carbamoyltetrazole product, mp 105-112°C.

EXAMPLE 35

5-Methoxy-1-phenyl-1H-indole-2-carboxylic acid

A mixture of 60.0 g (0.32 mole) of 5-methoxy-1H-indole-2-carboxylic acid, 35.0 ml (52.2 g; 0.32 mole) of bromobenzene, 36.0 g (0.64 mole) of potassium hydroxide, and 10.0 g (0.13 mole) of copper (II) oxide in 750 ml of N,N-dimethylformamide was stirred and heated at reflux under a nitrogen atmosphere for six hours. The cooled reaction mixture was added to 1.5 kg of ice/water and filtered through a bed of Celite filter-aid. Acidification of the filtrate with dilute hydrochloric acid precipitated the product. The solid was filtered and washed with water to yield 83.0g (95% yield) of crude acid product. A sample recrystallized from ether/hexane was analytically pure, mp 197-204°C.

EXAMPLE 36

5-Methoxy-1-phenyl-1H-indole-2-carboxylic acid, methyl ester

A solution of 30.0g (0.11 mole) of 5-methoxy-1-phenyl-1H-indole-2-carboxylic acid in 300 ml of N,N-dimethylformamide was treated with 9.6 g (0.12 mole) of 50% aqueous sodium hydroxide solution. The new mixture was stirred for 15 minutes, 8.0 ml (18.4g; 0.13 mole) of iodomethane was added, and stirring was continued at room temperature for four hours. The reaction mixture was added to 1.0 l of cold water and extracted with dichloromethane. The combined organic layers were washed twice with water, dried (anhydrous magnesium sulfate) and evaporated. Recrystallization of the residue from petroleum ether yielded 25 g (82% yield) of the analytically pure ester product, mp 67-68°C.

EXAMPLE 37

5-Methoxy-3-(methylsulfinyl)-1-phenyl-1H-indole-2-carboxylic acid, methyl ester

A mixture of 4.0 g (0.014 mole) of 5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, methyl ester in 7.0 ml (11.4g; 0.096 mole) of thionyl chloride (under a nitrogen atmosphere) was stirred at ambient temperature for ten minutes. After the addition of 50 ml of 20% hexane in ether solution, the new mixture was cooled in ice for 30 minutes to precipitate the crude intermediate sulfinyl chloride. The solid was filtered and washed with hexane to yield 3.0 g (63% crude yield) of 3-(chlorosulfinyl)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, methyl ester.

The total crude intermediate described above (3.0g; 0.0087 mole) was dissolved (under a nitrogen atmosphere) in 100 ml of tetrahydrofuran and cooled to -70°C. After dropwise addition of 15.0 ml (0.015 mole) of methyl magnesium bromide (1.0 M in ether), the new mixture was stirred at -70°C for 15 minutes, then quenched by the careful addition of 10.0 ml of

10% aqueous hydrochloric acid. The product was extracted with ether, and the combined organic layers were washed several times with brine and dried (anhydrous magnesium sulfate). Evaporation of the ether solution yielded an oil which was subjected to flash chromatography (silica gel, 50% ethyl acetate/chloroform elution) to yield 2.7 g (57% yield) of the analytically pure methylsulfinyl indole product, mp 140-144°C.

By variation of the Grignard reagent employed in the second part of the above procedure, also prepared were:

5-Methoxy-3-[(1-methylethyl)sulfinyl]-1-phenyl-1H-indole-2-carboxylic acid, methyl ester), mp 103-104°C;

and

5-Methoxy-1-phenyl-3-(phenylsulfinyl)-1H-indole-2-carboxylic acid, methyl ester, mp 146-148°C.

EXAMPLE 38

5-Methoxy-3-(methylthio)-1-phenyl-1H-indole-2-carboxylic acid

A mixture of 8.0 g (0.023 mole) of 5-methoxy-3-(methylsulfinyl)-1-phenyl-1H-indole-2-carboxylic acid, methyl ester and 10.0 g (0.067 mole) of sodium iodide in 200 ml of acetone (under a nitrogen atmosphere) was maintained at 0-5°C and treated dropwise with 10.0 ml (14.9g; 0.071 mole) of trifluoroacetic anhydride. The reaction mixture was stirred for ten minutes, then poured into 300 ml of ice/5% sodium bicarbonate solution. The product was extracted with ether, and the combined extracts were washed with 5% aqueous sodium thiosulfate solution, followed by brine. The organic layer was dried (anhydrous magnesium

sulfate) and evaporated to yield 7.5 g (100% yield) of crude intermediate 5-methoxy-3-(methylthio)-1-phenyl-1H-indole-2-carboxylic acid, methyl ester as an oil.

The total crude intermediate ester described above (7.5g, 0.023 mole) was dissolved in 200 ml of methanol and treated with 55.0 ml (0.11 mole) of 2.0 N aqueous sodium hydroxide solution. The mixture was stirred at 60° for 2.5 hours, cooled, and added to 500 g ice/water. Acidification with 10% hydrochloric acid followed by filtration and washing with water yielded 5.0 g (67% yield) of the analytically pure carboxylic acid product, mp 161-163°C (dec.).

Similarly prepared by the above procedures from the appropriate sulfinyl esters were:

5-Methoxy-1-phenyl-3-(phenylthio)-1H-indole-2-carboxylic acid, mp 153-156°C and

5-Methoxy-3-[(1-methylethyl)thio]-1-phenyl-1H-indole-2-carboxylic acid and

5-Methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-1H-indole-2-carboxylic acid; the latter two compounds were non-crystalline and were converted to the carbamoyltetrazoles without extensive purification.

EXAMPLE 39

5-Methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol -5-yl-1H-indole-2-carboxamide

A mixture of 1.2 g (0.0038 mole) of 5-methoxy-3-(methylthio)-1-phenyl-1H-indole-2-carboxylic acid and 0.74 g (0.0046 mole) of 1,1'-carbonylbis (1H-imidazole) in 50 ml of acetonitrile was stirred at 50°C under a nitrogen atmosphere for one hour. The reaction mixture was cooled slightly and treated with

a mixture of 0.40 g (0.0047 mole) of anhydrous 5-aminotetrazole and 1.1 ml (0.80 g; 0.0079 mole) of triethylamine in 25 ml of warm acetonitrile. The new mixture was then stirred at 50° for 16 hours, cooled, and added to 200 g of ice/H_2O. Acidification to pH 4 with acetic acid precipitated the crude product, which was filtered and washed with water. Recrystallization from 30% acetonitrile in 2-propanol yielded 0.92 g (64% yield) of analytically pure carbamoyltetrazole product, mp 252-253°C.

Similarly prepared by the above procedure from the appropriate carboxylic acid were:

5-Methoxy-3-[(1-methylethyl)thio]-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide mp 247-250°C (dec.);

5-Methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide mp 254-256°C (dec.) and

5-Methoxy-1-phenyl-3-(phenylthio)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 243-245°C (dec.).

EXAMPLE 40

5-Methoxy-3-(methylsulfonyl)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

A solution of 1.2g (0.0032 mole) of 5-methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide in 75 ml of water containing 0.27 g (0.0032 mole) of sodium bicarbonate was treated with a slurry of 2.0 g (0.013 mole) of potassium permanganate in 75 ml of acetone. After stirring at ambient temperature for two hours, the mixture was filtered through a bed of Celite filter-aid. The filtrate

was cooled in ice and acidified to pH 4 with acetic acid to precipitate the crude sulfone product. The solid was filtered, washed with water, and recrystallized from 2-propanol/acetonitrile/water (10/20/1) to yield 0.38 g (28% yield) of the analytically pure sulfone product, mp 263°C dec.

EXAMPLE 41

5-Methoxy-3-[(1-methylethyl)sulfonyl]-1-phenyl-1H-indole-2-carboxylic acid

A solution of 3.0 g (0.0081 mole) of 5-methoxy-3-[(1-methylethyl)sulfinyl]-1-phenyl-1H-indole-2-carboxylic acid, methyl ester in 250 ml of acetone was treated with a slurry of 2.6 g (0.016 mole) of potassium permanganate in 50 ml of water. After stirring at ambient temperature for four hours, the excess oxidant was destroyed by the addition of solid potassium iodide. The reaction mixture was filtered through a bed of Celite filter-aid, and a volume of water equivalent to that of the filtrate was added. The precipitated solid was filtered and washed with water to yield 1.2 g (40% yield) of intermediate sulfone 5-methoxy-3-[1-methylethyl)sulfonyl]-1-phenyl-1H-indole-2-carboxylic acid, methyl ester, mp 164-166°C.

A 1.0 g (0.0026 mole) sample of the above sulfone ester was saponified with sodium hydroxide as described in Example 38 to yield 0.75 g (77% yield) of the corresponding sulfone carboxylic acid, mp 171-173°C.

EXAMPLE 42

5-Methoxy-3-[(1-methylethyl)sulfinyl]-1-phenylmethyl 1H-indole-2-carboxylic acid, ethyl ester

A suspension of 7.0 g (0.023 mole) of 5-methoxy-1-phenylmethyl-1H-indole-2-carboxylic acid, ethyl ester (Y. Murakami, et al, Synthesis, 738 (1984)) in 75 ml of n-heptane under an argon atmosphere was cooled in ice and treated with 15.0 ml (24.5 g; 0.21 mole) of thionyl chloride. The mixture was stirred for 30 minutes, and the precipitated sulfinyl chloride intermediate was filtered and washed several times with hexane to yield 7.3 g (76% yield) of 3-(chlorosulfinyl)-5-methoxy-1-phenylmethyl-1H-indole-2-carboxylic acid, ethyl ester.

The total crude intermediate described above was treated with isopropylmagnesium bromide in a manner analagous to that described in Example 37. Flash chromatographic purification (silica gel, 10% ethyl acetate in hexane elution) of the initial oil product yielded 4.2 g (46% yield) of the analytically pure (1-methylethyl)sulfinyl indole ester product, mp 97-99°C.

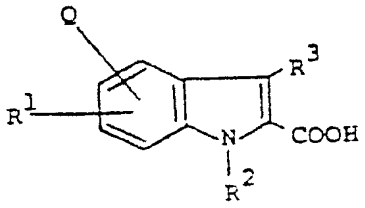
EXAMPLE 43

3-(Diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid

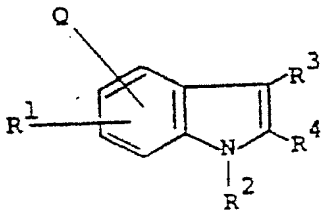
A mixture of 2.4 g (0.0066 mole) of 3-(diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, ethyl ester (prepared as described in Example 34), and 1.6 g (0.040 mole) of sodium hydroxide in 50 ml of ethanol plus 15 ml of water was stirred at 65° for four hours. The reaction mixture was cooled, added to 250 g ice/brine, and acidified to pH 2 with dilute hydrochloric acid. The product was extracted with

ether, and the combined organic layers were washed twice with brine and dried (anhydrous magnesium sulfate). Evaporation of the ether solution left a solid residue, which was triturated with ether/hexane to yield 1.55 g (70% yield) of the crude acid product. A sample recrystallized from ether/hexane was analytically pure, mp 141-143°C.

SCHEME I

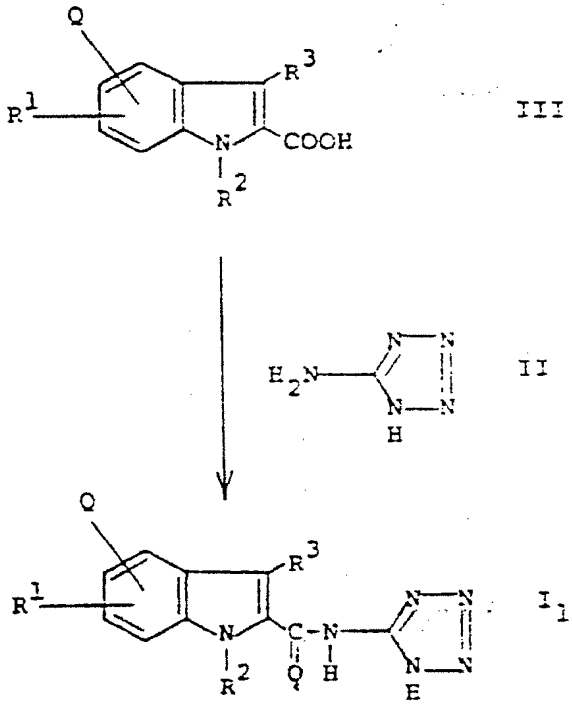


III

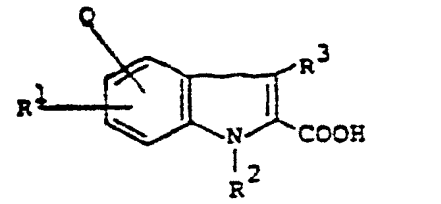


I

SCHEME II



SCHEME III

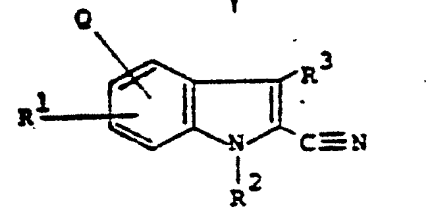


III

Step I

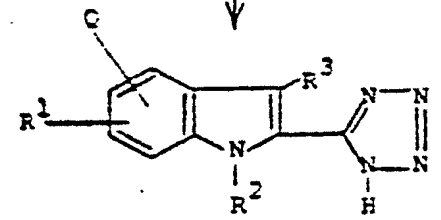
1) H_2NR

2) $-H_2O$



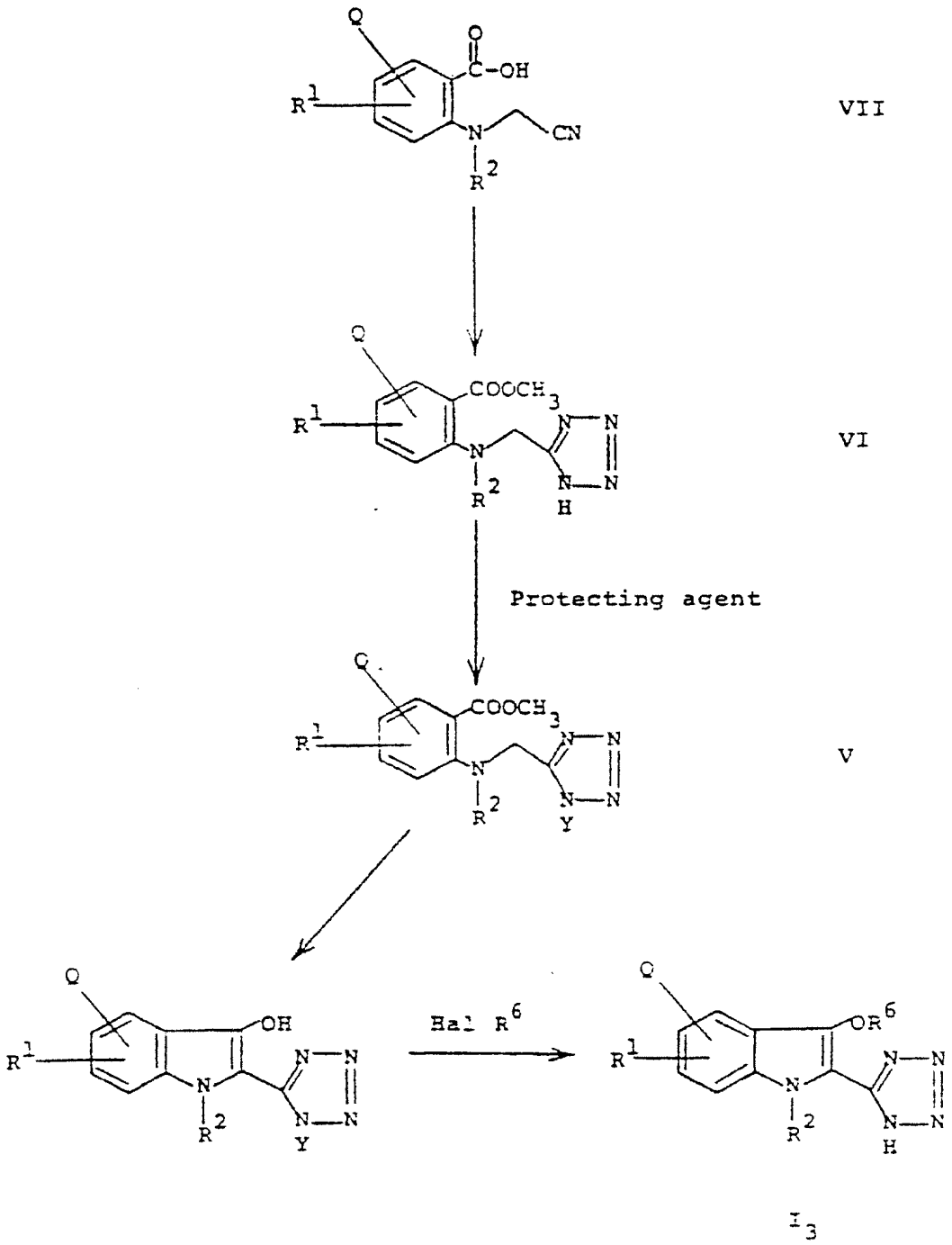
IV

Step II

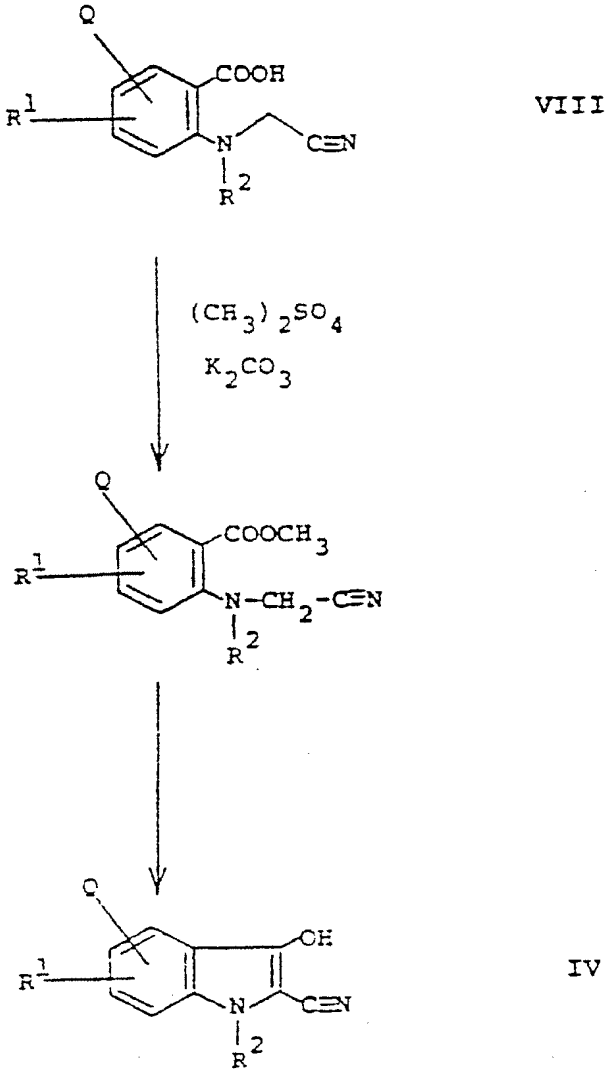


I_2

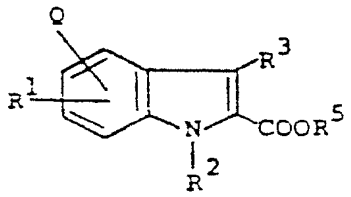
SCHEME IV


Q
O
C-OH
R1
N
CN
R2
VII
COOCH3
N
N
N
N
H
VI
Protecting agent
Y
V
OH
Hal R6
OR6
I3

SCHEME V



SCHEME VI

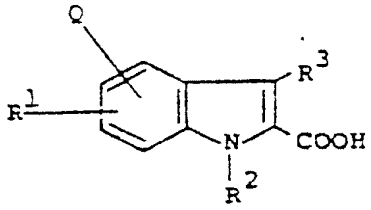


IX

1) KOH; 2) E^+

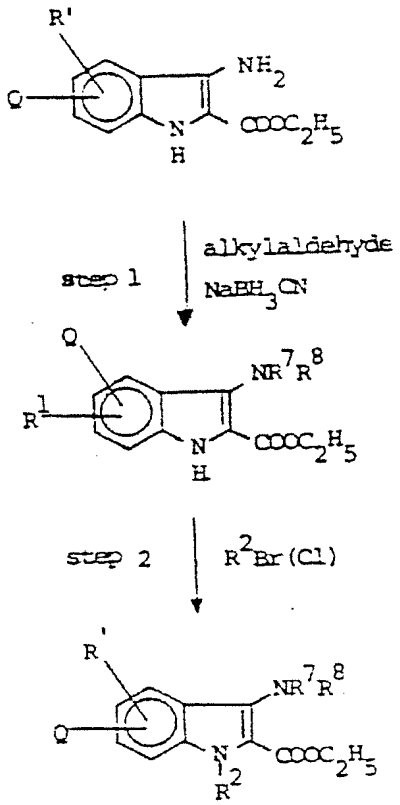
or

1) KO-t, DMSO; 2) H^+



III

SCHEME VII

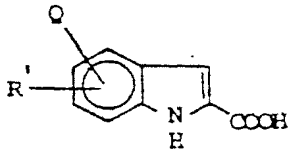


XX

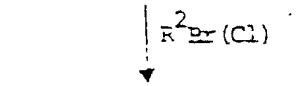
XXI

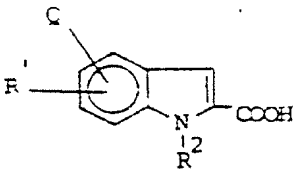
IX1

SCHEME VIII

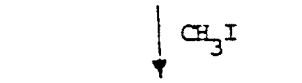


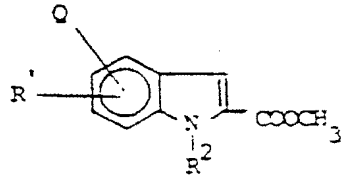
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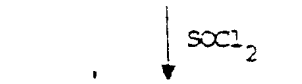


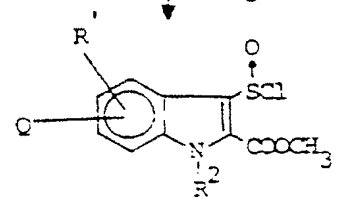
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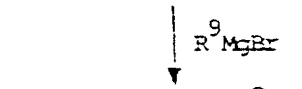


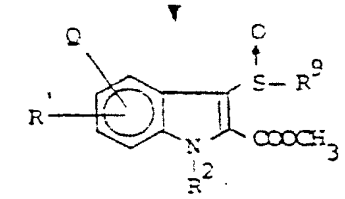
XXXII





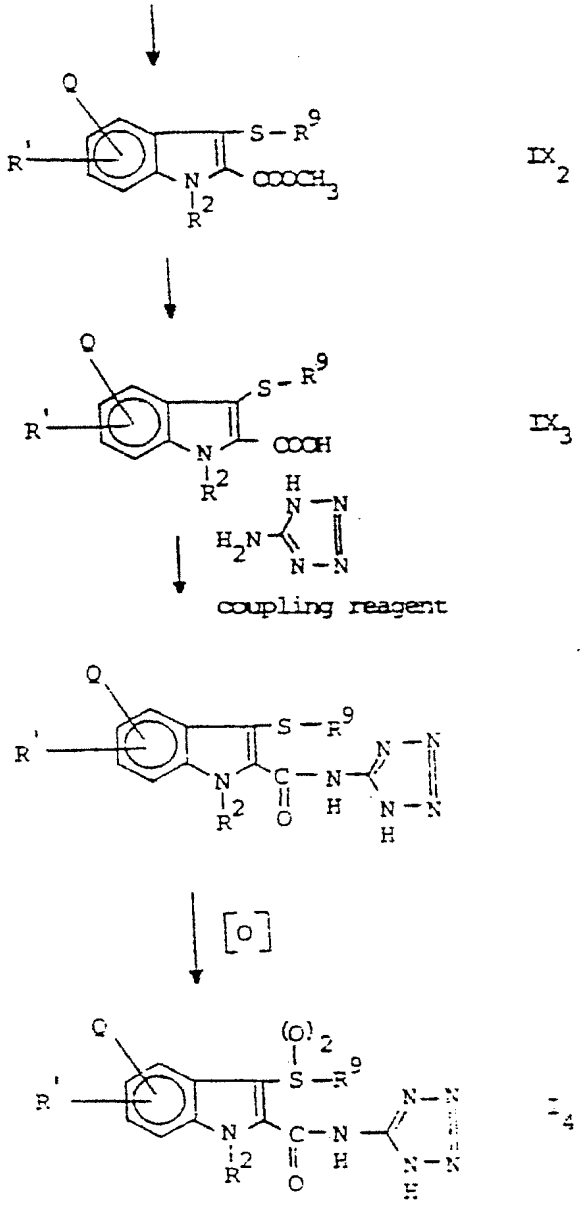
XXXIII





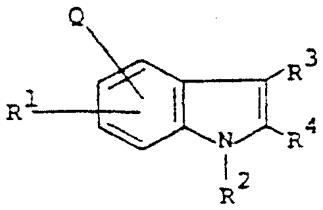
XXXIV

SCHEME VIII (CONT'D)

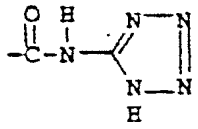


EIN-1

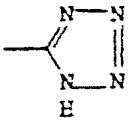
FORMULA



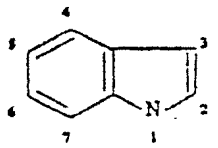
I



A



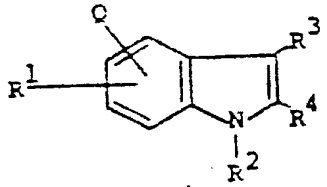
B



I^1

CLAIMS (for BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. A compound having the following general formula (I) :



(I)

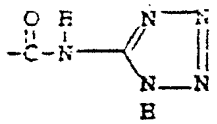
and pharmaceutically acceptable salts thereof, wherein:

R^1 and Q are each, independently, H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, an alkylsulphinyl having from one to four carbon atoms, an alkylsulphonyl having from one to four carbon atoms, a hydroxy group, a nitro group, an amino group, a substituted amino group or a halogen, R^1 being further chosen from a methylenedioxy radical attached to adjacent carbon atoms of the benzene ring;

R^2 is H, an alkyl having from one to twelve carbon atoms, a phenyl radical, a substituted phenyl radical or a benzyl radical;

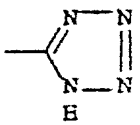
R^3 is H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, a phenylthio radical, a substituted phenylthio radical, an alkylsulphinyl having from one to four carbon atoms, a phenylsulphinyl radical, a substituted phenylsulphinyl radical, an alkylsulphonyl having from one to four carbon atoms, a phenylsulphonyl radical, a substituted phenylsulphonyl radical, an amino group, or a substituted amino group; and

R^4 is



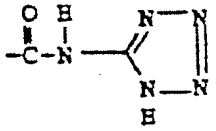
(A)

or



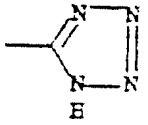
(B)

2. A compound according to Claim 1, wherein R^4 is



(A)

3. A compound according to Claim 1, wherein R^4 is



(B)

4. A compound according to Claim 2, wherein R^3 is alkoxy.

5. A compound according to Claim 4, having one of the following names:

3-methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

1-hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

3-methoxy-1-nonyl-N1H-tetrazol-5-yl-1H-indole-carboxamide;

3-methoxy-1-(phenylmethyl)-1N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

3-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

1-phenyl-3(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

1-(4-methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

5-chloro-3-(1-methylethoxy)-1phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;

5-methoxy-1-methyl-3(1-methylethoxy)-N-1H-tetrazol-5-

yl-1H-indole-2-carboxamide;
3,5-dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1-1H-indole-2-carboxamide;
5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
3-(n-dodecyloxy)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl--1H-indole-2-carboxamide.

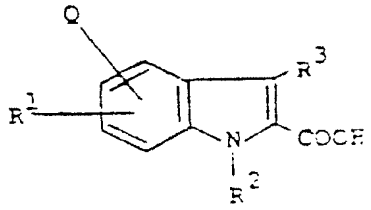
6. A compound according to Claim 2 having one of the following names:
3-(diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1-H-indole-2-carboxamide;
5-methoxy-3-[(1-methylethyl)thio]-1phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-1-phenyl-3(phenylthio)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-3-(methylsulphony)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
5-methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

7. A pharmaceutical composition comprising an effective amount of a compound according to any preceding claim in admixture with a pharmaceutically acceptable carrier or diluent.

8. For use in a method of treating allergies in mammals, a compound as claimed in any one of Claims 1

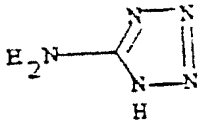
to 6 or a pharmaceutical composition as claimed in Claim 7.

9. A process for the preparation of a compound of formula I as defined in Claim wherein R^4 is A, which comprises reacting a compound of the Formula (III)



(III)

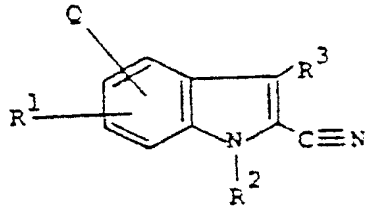
wherein R^1, Q, R^2, and R^3 are as defined in Claim 1 with a compound of Formula (II)



(II)

in the presence of a coupling agent.

10. A process for the preparation of a compound of formula I as defined in Claim 1 wherein R^4 is B which comprises treating a compound of Formula (IV)

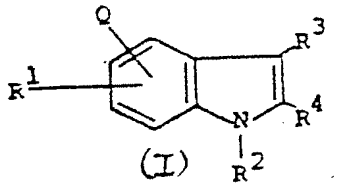


(IV)

wherein R^1, Q, R^2, and R^3 are as defined in Claim 1 above by a known method or a variant thereof

CLAIMS (for AT)

1. A process for preparing a compound having the following general formula (I) :



(I)

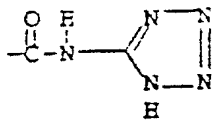
and pharmaceutically acceptable salts thereof, wherein:

R^1 and Q are each, independently, H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, an alkylsulphinyl having from one to four carbon atoms, an alkylsulphonyl having from one to four carbon atoms, a hydroxy group, a nitro group, an amino group, a substituted amino group or a halogen, R^1 being further chosen from a methylenedioxy radical attached to adjacent carbon atoms of the benzene ring;

R^2 is H, an alkyl having from one to twelve carbon atoms, a phenyl radical, a substituted phenyl radical or a benzyl radical;

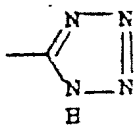
R^3 is H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, a phenylthio radical, a substituted phenylthio radical, an alkylsulphinyl having from one to four carbon atoms, a phenylsulphinyl radical, a substituted phenylsulphinyl radical, an alkylsulphonyl having from one to four carbon atoms, a phenylsulphonyl radical, a substituted phenylsulphonyl radical, an amino group, or a substituted amino group; and

R^4 is



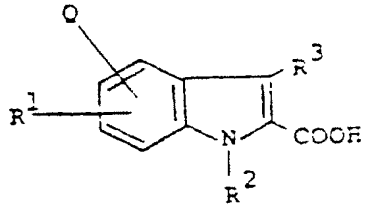
(A)

or



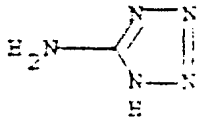
(B)

which process comprises reacting a compound of the Formula (II)



(III)

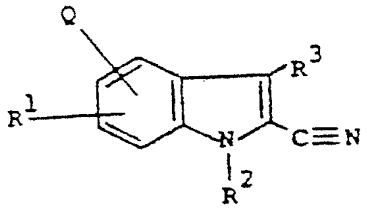
wherein R^1, Q, R^2, and R^3 are as defined above with a compound of Formula (II)



(II)

in the presence of a coupling agent to form a compound of Formula (I) in which R^4 is A; or

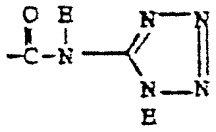
treating a compound of formula (IV)



(IV)

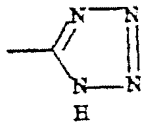
wherein R^7, Q, R^2, and R^3, are as defined above by a known method or variant thereof to form a compound of formula (I) in which R^4 is B; and, if desired, forming a pharmaceutically acceptable salt thereof.

2. A process according to Claim 1, wherein R^4 is



(A)

3. A process according to Claim 1, wherein R^4 is



(B)

4. A process according to Claim 2, wherein R^3 is alkoxy.

5. A process according to Claim 4, in which one

of the following compounds is prepared:
3-methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
1-hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-methoxy-1-nonyl-N1H-tetrazol-5-yl-1H-indole-carboxamide;
3-methoxy-1-(phenylmethyl)-1N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
1-phenyl-3(phenylmetnoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
1-(4-methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-chloro-3-(1-methylethoxy)-1phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-1-methyl-3(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3,5-dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1-1H-indole-2-carboxamide;
5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
3-methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
3-(n-dodecyloxy)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl--1H-indole-2-carboxamide.

6. A process according to Claim 2, in which one of the following compounds is prepared:
3-(diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1-H-indole-2-carboxamide;
5-methoxy-3-[(1-methylethyl)thio]-1phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-1-phenyl-3(phenylthio)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
5-methoxy-3-(methylsulphony)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
5-methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

7. A process for preparing a pharmaceutical composition which process comprises combining an effective amount of a compound prepared in accordance with any preceding claim together with a pharmaceutically acceptable carrier or diluent.

8. For use in a method of treating allergies in mammals, a compound prepared by a process as claimed in any one of Claims 1 to 6 or a pharmaceutical composition prepared by a process as claimed in Claim 7.

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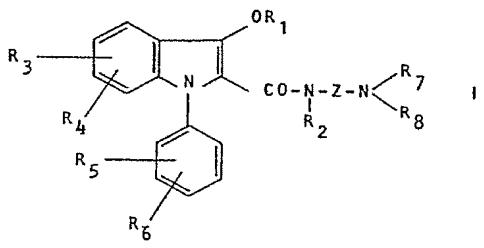
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(54) 1-Phenyl-2-aminocarbonylindol-Verbindungen sowie Verfahren zu ihrer Herstellung und diese Verbindungen enthaltende Arzneimittel.

(57) Neue 1-Phenyl-2-aminocarbonylindol-Verbindungen der allgemeinen Formel I



I

worin R_1 eine aliphatische oder aromatische Acylgruppe oder eine gegebenenfalls substituierte Benzylgruppe bedeutet, R_2 Wasserstoff oder niederes Alkyl bedeutet, R_3 Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy bedeutet. R_4 Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy bedeutet, R_5 die für R_3 und R_8 die für R_4 angegebene Bedeutungen besitzen oder R_5 Nitro oder Trifluormethyl bedeutet, falls R_5 Wasserstoff ist, R_7 und R_8 je Wasserstoff oder niederes Alkyl bedeuten oder zusammen mit dem Stickstoffatom eine heterocyclische Gruppe bilden, Z eine gegebenenfalls durch Hydroxy oder Acyloxy substituierte Alkylenkette bedeutet, werden beschrieben. Die Verbindungen besitzen pharmakologische, insbesondere antiarythmische Eigenschaften.

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KALI-CHEMIE PHARMA GMBH

1-Phenyl-2-aminocarbonylindol-Verbindungen sowie Verfahren zu ihrer Herstellung und diese Verbindungen enthaltende Arzneimittel

Die vorliegende Erfindung betrifft neue 3-Acyloxy- und 3-Benzyloxy-1-phenyl-2-alkylaminocarbonylindol-Verbindungen und deren Salze sowie diese Verbindungen enthaltende pharmazeutische Zubereitungen.

Das belgische Patent Nr. 701023 und das französische Patent Nr. 1503908 beschreiben 2-Carboxamidoindol-Verbindungen, welche antiemetische und zentraldämpfende Wirkungen zeigen, und die französischen Patente Nr. 1527M und 1313759 beschreiben 2-Carboxamidoindol-Verbindungen, welche ebenfalls antiemetische und daneben lokalanästhesierende und antifibrillatorische Eigenschaften besitzen.

Der Erfindung liegt die Aufgabe zugrunde, neue 1-Phenyl-2-aminocarbonylindol-Verbindungen mit wertvollen pharmakologischen Eigenschaften zu entwickeln.

Es wurde nun gefunden, daß die neuen in 3-Stellung durch Acyloxy oder Benzyloxy substituierten 1-Phenyl-2-aminocarbonylindol-Verbindungen wertvolle pharmakologische Wirkungen, insbesondere antiarrhythmische Wirkungen, besitzen und ein vorteilhaftes Wirkungsprofil mit guter therapeutischer Breite und geringer Toxizität aufweisen. Aufgrund

dieser Wirkungen sind die neuen Verbindungen als Arzneimittel, insbesondere zur Behandlung von Herz-Rhythmusstörungen, geeignet.

Die vorliegende Erfindung betrifft daher neue 1-Phenyl-2-aminocarbonylindol-Verbindungen der allgemeinen Formel I

(siehe Formel I)

worin

R_1 eine Alkanoylgruppe mit 2 bis 12 Kohlenstoffatomen bedeutet, welche gegebenenfalls substituiert sein kann durch eine Carboxyl- oder niedere Alkoxycarbonylgruppe oder niederes Alkoxy oder Benzyloxy, oder

R_1 eine Gruppe a

(siehe Formel a)

bedeutet, worin n 0, 1, 2 oder 3 ist und R_9 und R_{10} unabhängig voneinander Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy oder, falls sie an 2 benachbarte Kohlenstoffatome gebunden sind, auch gemeinsam Methylendioxy darstellen, oder, falls n 0 ist und R_9 Wasserstoff darstellt, R_{10} auch Nitro oder Trifluormethyl bedeutet, oder

R_1 Benzyl, welches gegebenenfalls substituiert sein kann durch 1 bis 2 Substituenten aus der Gruppe niederes Alkyl, niederes Alkoxy, Nitro und Halogen, bedeutet,

R_2 Wasserstoff oder niederes Alkyl bedeutet,

R_3 Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy bedeutet,

R_4 Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy bedeutet,

R_5 Wasserstoff, niederes Alkyl, Halogen oder niederes Alkoxy bedeutet,

R_6 Wasserstoff, niederes Alkyl, niederes Alkoxy, Halogen oder, falls R_5 Wasserstoff ist, auch Nitro oder Trifluormethyl bedeutet,

R_7 Wasserstoff oder niederes Alkyl bedeutet,

R_8 Wasserstoff oder niederes Alkyl bedeutet, oder

R_7 und R_8 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe b bilden,

(siehe Formel b)

worin

X für eine Bindung, $-CH_2-$, $-C_2H_4-$, O oder S steht,

Z eine Alkylenkette mit 2 bis 5 Kohlenstoffatomen bedeutet, welche gegebenenfalls an einem nicht an Stickstoff gebundenen Kohlenstoff durch Hydroxy oder R'_1O-Gruppe, worin R'_1 die für R_1 angegebene Bedeutung mit Ausnahme von gegebenenfalls substituiertem Benzyl besitzt, substituiert ist,

sowie deren Säureadditionssalze.

Sofern in den Verbindungen der Formel I die Substituenten R_3 bis R_6 der Phenylringe eine niedere Alkylgruppe enthalten, kann diese gerade oder verzweigt sein und insbesondere 1 bis 4 Kohlenstoffatome enthalten. So kommen insbesondere Methyl, Äthyl, n-Propyl, Isopropyl, n-Butyl oder tert.-Butyl, bevorzugt Methyl oder Äthyl in Frage. Insbesondere bei Disubstitutionen an den Phenylringen stellen alkylhaltige Substituenten vorzugsweise Methyl oder Methoxy dar.

Als Halogensubstituenten in den Phenylringen kommen insbesondere Fluor, Chlor oder Brom, bevorzugt Chlor oder Brom, in Frage.

Die Substituenten R_3 und R_4 stellen vorzugsweise Wasserstoff oder Halogen dar. Die Substituenten R_5 und R_6 stellen vorzugsweise Wasserstoff, Halogen oder niederes Alkyl dar.

Der Substituent R_2 steht insbesondere für Wasserstoff. Sofern R_2 niederes Alkyl bedeutet, enthält dieses 1 bis 4, insbesondere 1 bis 2 Kohlenstoffatome.

Falls R_7 und/oder R_8 eine niedere Alkylgruppe bedeuten, kann diese gerade oder verzweigt sein und insbesondere 1 bis 4 Kohlenstoffatome enthalten. Als Alkylgruppen kommen insbesondere Methyl-, Äthyl-, Propyl- und Butyl-Gruppen in Frage. Insbesondere steht die NR_7R_8-Gruppe für eine vorzugsweise unverzweigte Dialkylaminogruppe, beispielsweise die Diäthylamino-Gruppe.

Z stellt eine Alkylenkette mit 2 bis 5 Kohlenstoffatomen dar, vorzugsweise eine gerade Alkylenkette mit 2 bis 4 Kohlenstoffatomen. Falls Z eine durch Hydroxy oder R'_1O substituierte Alkylenkette bedeutet, stellt diese vorzugsweise eine 2-Hydroxypropylen- oder 2-R'_1O-Propylen-Kette dar.

Sofern eine Acylgruppe oder eine substituierte Benzylgruppe R_1 niederes Alkyl enthaltende Substituenten trägt, besitzen diese insbesondere 1 bis 4 Kohlenstoffatome und stellen vorzugsweise Methyl oder Äthyl dar.

Eine Acylgruppe R_1 stellt den Säurerest einer aliphatischen oder aromatischen Carbonsäure dar. Als aliphatische Carbonsäuren eignen sich niedere Monocarbonsäuren mit vorzugsweise 1 bis 4 Kohlenstoffatomen in der Alkylkette wie Essigsäure, Propionsäure oder Propan- und Butancarbonsäu-

ren. Ferner eignen sich substituierte niedere Carbonsäuren mit vorzugsweise 1 bis 4 Kohlenstoffatomen in der Alkylkette, z.B. niedere Dicarbonsäuren wie Bernsteinsäure oder deren niedere Monoalkylester, sowie durch niederes Alkoxy, insbesondere Methoxy oder Äthoxy, oder Benzyloxy substituierte Monocarbonsäuren. Auch gegebenenfalls substituierte geradkettige oder verzweigte aliphatische Carbonsäuren mit bis zu 11 z.B. 5 bis 11 Kohlenstoffatomen in der Alkylkette sind geeignet wie beispielsweise Capronsäure, Caprylsäure oder Laurinsäure.

Als aromatische Säuren eignen sich gegebenenfalls substituierte Phenylalkylcarbonsäuren mit bis zu 3 Kohlenstoffatomen in der Alkylenkette und insbesondere gegebenenfalls substituierte Benzoesäuren.

Als Beispiele von geeigneten Acylresten R_4 seien genannt Acetyl, Propionyl, Isobutyryl, Valeroyl, Pivaloyl, Isovaleroyl, Dodecanoyl, Benzoyl, Chlorbenzoyl, Nitrobenzoyl, Methylbenzoyl, Methoxybenzoyl, Phenylacetyl, Hydroxycarbonyläthylcarbonyl, Methoxycarbonyläthylcarbonyl.

So gehören zu den erfindungsgemäßen Verbindungen unter anderen:

2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-pivaloyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-propionyloxypropylaminocarbonyl]-3-propionyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-isobutyryloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-dodecanoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-benzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-o-chlorbenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-

3-m-chlorbenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-p-chlorbenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-p-nitrobenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-p-methylbenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-p-methoxybenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-m,p-dimethoxybenzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-phenylacetoxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-benzyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-methoxycarbonylmethylcarbonyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-hydroxycarbonyläthylcarbonyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-methoxycarbonyläthylcarbonyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-benzoyloxy-1-(4-chlorphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-methoxyacetoxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-benzoyloxypropylaminocarbonyl]-
3-benzoyloxy-1-(4-chlorphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-acetoxypropylaminocarbonyl]-
3-acetoxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-benzoyloxypropylaminocarbonyl]-
3-benzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-pivaloyloxy-1-phenyl-5-bromindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-pivaloyloxy-1-phenyl-4-chlorindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-pivaloyloxy-1-(4-methoxyphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-

3-pivaloyloxy-1-(4-fluorphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-pivaloyloxy-1-(4-methoxyphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-propionyloxypropylaminocarbo-
nyl]-3-propionyloxy-1-phenyl-5-bromindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-benzoyloxy-1-phenyl-4-chlorindol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-benzoyloxy-1-(4-fluorphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-pivaloyloxy-1-(4-chlorphenyl)-indol,
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-
3-benzoyloxy-1-(4-methoxyphenyl)-indol,
2-(3-Pyrrolidino-2-hydroxypropylaminocarbonyl)-
3-pivaloyloxy-1-phenylindol,
2-(3-Pyrrolidino-2-benzoyloxypropylaminocarbonyl)-
3-benzoyloxy-1-phenylindol,
2-(3-Morpholino-2-hydroxypropylaminocarbonyl)-
3-pivaloyloxy-1-phenylindol,
2-(3-Morpholino-2-hydroxypropylaminocarbonyl)-
3-benzoyloxy-1-phenylindol,
2-[2-(N,N-Dimethylamino)-äthylaminocarbonyl]-
3-acetoxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-propylaminocarbonyl]-
3-acetoxy-1-phenylindol,
2-[4-(N,N-Diäthylamino)-butylaminocarbonyl]-
3-acetoxy-1-phenylindol,
2-[2-(N,N-Dimethylamino)-äthylaminocarbonyl]-
3-propionyl-1-phenylindol,
2-[3-(N,N-Diäthylamino)-propylaminocarbonyl]-
3-propionyloxy-1-phenylindol,
2-[4-(N,N-Diäthylamino)-butylaminocarbonyl]-
3-propionyloxy-1-phenylindol,
2-[2-(N,N-Dimethylamino)-äthylaminocarbonyl]-
3-benzoyloxy-1-phenylindol,
2-[3-(N,N-Diäthylamino)-propylaminocarbonyl]-
3-benzoyloxy-1-phenylindol,
2-[4-(N,N-Diäthylamino)-butylaminocarbonyl]-

3-benzoyloxy-1-phenylindol,
2-[2-(N,N-Dimethylamino)-äthylaminocarbonyl]-
3-pivaloyloxy-1-(2,3-dimethylphenyl)-indol,
2-[3-(N,N-Dimethylamino)-propylaminocarbonyl]-
3-pivaloyloxy-1-(4-chlorphenyl)-indol,
2-[2-(N,N-Dimethylamino)-äthylaminocarbonyl]-
3-pivaloyloxy-1-(4-chlorphenyl)-indol,
2-[2-(N,N-Diäthylamino)-äthylaminocarbonyl]-
3-pivaloyloxy-1-phenyl-5-bromindol,

Die neuen 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen der Formel Ia

(siehe Formel Ia)

worin R'_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, und Z obige Bedeutung besitzen, und deren Säureadditionssalze können erhalten werden, indem man in an sich bekannter Weise Verbindungen der allgemeinen Formel II

(siehe Formel II)

worin
R_2, R_3, R_4, R_5, R_6, R_7 und R_8 obige Bedeutung besitzen und Z' eine Alkylenkette mit 2 bis 5 Kohlenstoffatomen bedeutet, welche gegebenenfalls an einem nicht an Stickstoff gebundenen Kohlenstoff durch Hydroxy substituiert ist, mit einem Säurederivat der allgemeinen Formel III

$$R'_1 - X \qquad III$$

worin
R'_1 obige Bedeutung besitzt und X eine reaktive Gruppe bedeutet oder, sofern R'_1 eine freie Carboxylgruppe enthält, auch einem cyclischen Anhydrid einer Säure R'_1OH acyliert und gegebenenfalls freie Verbindungen der Formel Ia in ihre Säureadditionssalze überführt oder die Säureadditionssalze in die freien Verbindungen der Formel Ia überführt.

Die Umsetzung der Säurederivate der Formel III oder der cyclischen Anhydride mit den Hydroxyverbindungen der Formel II kann nach an sich zur Esterbildung durch Acylierung üblichen Methoden ausgeführt werden. Als reaktionsfähige Derivate kommen insbesondere Säurehalogenide, vorzugsweise -chloride, Ester und Anhydride oder gemischte Anhydride der Säuren der R'_1OH in Frage, z.B. Verbindungen der Formel III, worin die reaktive Gruppe X Halogen, insbesondere Chlor oder Brom, eine Gruppe OR'_1, worin R'_1 obige Bedeutung besitzt, oder eine Gruppe O-CO-W bedeutet, worin W für niederes Alkyl oder niederes Alkoxy steht. Die Acylierung kann in einem unter den Reaktionsbedingungen inerten Lösungsmittel bei Temperaturen zwischen Raumtemperatur und dem Siedepunkt des Lösungsmittels erfolgen. Als Lösungsmittel eignen sich halogenierte Kohlenwasserstoffe wie Methylenchlorid oder Chloroform, aromatische Kohlenwasserstoffe wie Benzol, Toluol, Xylol oder Chlorbenzol, cycli-

sche Äther wie Tetrahydrofuran oder Dioxan, Dimethylformamid oder Gemische dieser Lösungsmittel.

Die Acylierung wird zweckmäßig in Gegenwart eines säurebindenden Reagenzes durchgeführt. Als säurebindende Mittel eignen sich anorganische Basen, insbesondere Alkalimetallcarbonate und -hydroxyde wie z.B. Kaliumcarbonat oder Kaliumhydroxyd oder organische Basen, insbesondere tertiäre Niederalkylamine und Pyridine wie z.B. Triäthylamin oder 4-Dimethylaminopyridin.

Falls die Ausgangsverbindungen außer der zu veresternden Hydroxygruppe in 3-Stellung noch eine weitere freie Hydroxygruppe in dem Seitenkettenglied Z' enthalten, findet unter den vorstehenden Acylierungsbedingungen die Acylierung bevorzugt an der enolischen Hydroxygruppe in 3-Stellung statt. Je nach Menge des eingesetzten Säurederivates und der Reaktionsdauer kann jedoch die Hydroxygruppe in der Seitenkette ganz oder teilweise ebenfalls zu einer R'$_1$O-Gruppe acyliert werden. Allfällige Gemische von mono-und diacylierten Verbindungen der Formel Ia lassen sich auf an sich bekannte Weise, z.B. durch Chromatographie, trennen.

Zur Herstellung von Verbindungen der Formel Ia, welche eine freie Hydroxygruppe in dem Seitenkettenglied Z enthalten, kann auch in den entsprechenden Ausgangsverbindungen der Formel II die freie Hydroxygruppe in dem Glied Z' gewünschtenfalls vor der Umsetzung in an sich bekannter Weise mit einer Schutzgruppe versehen sein, welche anschließend leicht wieder abspaltbar ist unter Bedingungen, unter denen die Estergruppe in 3-Stellung nicht angegriffen wird. Beispielsweise eignen sich zum Schutz einer sekundären aliphatischen Hydroxygruppe leicht spaltbare Carbonate wie Benzylcarbonat.

Die neuen Verbindungen der Formel Ib

(siehe Formel Ib)

worin R_2, R_3, R_4, R_5, R_6, R_7, R_8 und Z obige Bedeutung besitzen und R_1'' Benzyl, welches gegebenenfalls substituiert sein kann durch 1 bis 2 Substituenten aus der Gruppe niederes Alkyl, niederes Alkoxy und Halogen, bedeutet, und deren Säureadditionssalze können erhalten werden, indem man Verbindungen der Formel Va

(siehe Formel Va)

worin R_3, R_4, R_5, R_6 und R_1'' obige Bedeutung besitzen, und X' eine reaktive Gruppe bedeutet, mit einer Verbindung der Formel VI

(siehe Formel VI)

worin R_2, R_7, R_8 und Z' obige Bedeutung besitzen, umsetzt, und gewüschtenfalls in erhaltenen Verbindungen der Formel Ib, worin Z eine freie Hydroxygruppe enthält, diese in an sich bekannter Weise acyliert und/oder gegebenenfalls freie Verbindungen der Formel Ib in ihre Säureadditionssalze überführt oder die Säureadditionssalze in die freien Verbindungen der Formel Ib überführt.

Die Umsetzung der Säurederivate der Formel Va mit Aminen der Formel VI kann nach an sich zur Bildung von Amid-Gruppierungen durch Aminoacylierung üblichen Methoden ausgeführt werden. Als reaktionsfähige Derivate kommen insbesondere Säurehalogenide, vorzugsweise -chloride, Ester und gemischte Anhydride in Frage, z.B. Verbindungen der Formel Va, worin die reaktive Gruppe X' Halogen, insbesondere Chlor oder Brom, niederes Alkoxy, insbesondere Alkoxy mit 1 bis 4 Kohlenstoffatomen, oder eine Gruppe O-CO-W bedeutet, worin W für niederes Alkyl oder niederes Alkoxy steht. Aus der Peptidchemie sind weitere zur Amidbildung geeignete Säurederivate bekannt, welche durch Umsetzen der entsprechenden Säuren mit bekannten Kopplungsreagentien auf bekannte Weise gebildet werden können (siehe z.B. Mukayama in Angew. Chemie 91, S. 789 - 812). Die Aminoacylierung kann in einem unter den Reaktionsbedingungen inerten Lösungsmittel bei Temperaturen zwischen Raumtemperatur und dem Siedepunkt des Lösungsmittels erfolgen. Als Lösungsmittel eignen sich halogenierte Kohlenwasserstoffe wie Methylenchlorid oder Chloroform, aromatische Kohlenwasserstoffe wie Benzol, Toluol, Xylol oder Chlorbenzol, cyclische Äther wie Tetrahydrofuran oder Dioxan, Dimethylformamid oder Gemische dieser Lösungsmittel.

Die Aminoacylierung kann gegebenenfalls, insbesondere wenn ein Säurehalogenid oder -anhydrid der Formel Va verwendet wird, in Gegenwart eines säurebindenden Reagenzes durchgeführt werden. Als säurebindende Mittel eignen sich anorganische Basen, insbesondere Alkalimetallcarbonate und -hy-

droxyde wie z.B. Natrium- oder Kaliumcarbonat oder Kaliumhydroxyd oder organische Basen, insbesondere tertiäre Niederalkylamine und Pyridine wie z.B. Triäthylamin, Pyridin oder 4-Dimethylaminopyridin. Statt einer Fremdbase kann auch ein Überschuß des Amins der Formel VI verwendet werden. Im Überschuß eingesetzte organische Basen können gleichzeitig auch als Lösungsmittel dienen.

Eine Acylierung einer freien OH-Gruppe in der Seitenkette von Verbindungen der Formel Ib kann auf an sich bekannte Weise, z.B. nach den für die Acylierung von Verbindungen der Formel II zu Verbindungen der Formel Ia angegebenen Methoden, erfolgen.

Verbindungen der Formel I, worin Z eine Hydroxy- oder Acyloxygruppe enthält, werden bei der Synthese in Form ihrer Racemate erhalten. Unter den Schutz dieser Erfindung fallen die racemischen Gemische wie auch die optisch aktiven Formen dieser Verbindungen. Die optisch aktiven Verbindungen können aus den racemischen Gemischen in an sich bekannter Weise durch Umsetzung mit geeigneten optisch aktiven Säuren, wie beispielsweise Weinsäure, O,O'-Dibenzoyl-Weinsäure, Mandelsäure, Di-O-isopropyliden-2-oxo-L-gulonsäure, und anschließende fraktionierte Kristallisation der gewonnenen Salze in ihre optisch aktiven Antipoden aufgetrennt werden.

Die Auftrennung in die optisch aktiven Verbindungen kann gewünschtenfalls auch in einer geeigneten Vorstufe, z.B. den Verbindungen der Formel II, erfolgen.

Die Verbindungen der Formel I können auf an sich bekannte Weise aus dem Reaktionsgemisch isoliert und gereinigt werden. Säureadditionssalze können in üblicher Weise in die freien Basen überführt werden, und diese gewünschtenfalls in bekannter Weise in pharmakologisch verträgliche Säureadditionssalze überführt werden.

Als pharmakologisch annehmbare Säureadditionssalze der Verbindungen der Formel I eignen sich beispielsweise deren Salze mit Chlorwasserstoffsäure, Bromwasserstoffsäure, Schwefelsäure, Phosphorsäure, Methansulfonsäure, Äthansulfonsäure, Cyclohexylaminosulfonsäure, Amidosulfonsäure, Essigsäure, Milchsäure, Weinsäure, Phenylessigsäure oder Mandelsäure. Sofern in dem Rest R_1 der Verbindungen der Formel I noch eine freie COOH-Gruppe enthalten ist, können die Verbindungen auch innere Salze bilden.

Die Ausgangsverbindungen der Formel II können erhalten werden, indem man aus Verbindungen der Formel IV

(siehe Formel IV)

worin R_2, R_3, R_4, R_5, R_6, R_7, R_8 und Z' obige Bedeutung besitzen und R_{11} Methyl oder eine hydrogenolytisch abspaltbare Gruppe, z.B. eine gegebenenfalls substituierte Benzylgruppe, bedeutet, die Hydroxygruppe in 3-Stellung auf an sich bekannte Weise freisetzt.

Die Spaltung der OR_{11}-Gruppe kann nach an sich zur Ätherspaltung üblichen Methoden erfolgen. Benzyläther lassen sich z.B. hydrogenolytisch spalten.

Verbindungen der Formel II können auch erhalten werden, indem man Verbindungen der Formel X

(siehe Formel X)

worin R_3, R_4, R_5 und R_6 obige Bedeutung besitzen und R_{12} niederes Alkyl bedeutet, mit Verbindungen der Formel VI umsetzt. Die Umsetzung kann auf an sich zur Esteraminolyse bekannte Weise, z.B. nach den hierzu u.a. zur Umsetzung der Verbindungen der Formel Va mit Verbindungen der Formel VI angegebenen Methoden erfolgen.

Die Ausgangsverbindungen der Formel IV können auf an sich bekannte Weise hergestellt werden, indem man Verbindungen der Formel V

(siehe Formel V)

worin R_3, R_4, R_5, R_6, R_{11} und X' obige Bedeutung besitzen, mit einer Verbindung der Formel VI umsetzt. Die Umsetzung kann nach den vorgehend zur Umsetzung von Verbindungen der Formel Va mit Verbindungen der Formel VI angegebenen Methoden auf an sich bekannte Weise erfolgen.

Verbindungen der Formel Vb

(siehe Formel Vb)

worin R_3, R_4, R_5, R_6, R_{11} und R_{12} obige Bedeutung besitzen, können auf an sich bekannte Weise erhalten werden, indem man

a') Verbindungen der Formel VII

(siehe Formel VII)

worin R_3, R_4, R_5, R_6 und R_{12} obige Bedeutung besitzen, in an sich bekannter Weise cyclisiert zu Verbindungen der Formel X und diese auf an sich bekannte Weise, z.B. nach zur Verätherung üblichen Methoden, in Verbindungen der Formel Vb überführt oder

b') zur Herstellung von Verbindungen der Formel Vb Verbindungen der Formel VIII

(siehe Formel VIII)

worin R_3, R_4, R_{11} und R_{12} obige Bedeutung besitzen, mit Verbindungen der Formel IX

(siehe Formel IX)

worin R_5 und R_6 obige Bedeutung besitzen und Hal Halogen bedeutet, umsetzt.

Die Verbindungen der Formel Vb können anschließend auf an sich bekannte Weise zu den entsprechenden Säuren hydrolysiert und diese in an sich bekannter Weise in weitere reaktionsfähige Säurederivate überführt werden. Die Überführung der freien Säuren in reaktive Säurederivate erfolgt ebenfalls auf an sich bekannte Weise. So können Säurehalogenide der Formel V zum Beispiel durch Umsetzung der Säuren mit einem anorganischen Säurehalogenid erhalten werden. Gemischte Säureanhydride können zum Beispiel durch Umsetzung von Alkalimetallsalzen der Säuren mit einem entsprechenden organischen Säurechlorid in Gegenwart einer tertiären organischen Base erhalten werden.

Die Cyclisierung der Verbindungen der Formel VII gemäß Verfahrensvariante a') wird zweckmäßigerweise in einem unter den Reaktionsbedingungen inerten Lösungsmittel in Gegenwart einer starken Base bei erhöhter Temperatur, beispielsweise bei Temperaturen zwischen 50 und 150 °C, durchgeführt. Als starke Basen eignen sich beispielsweise niedere Alkalimetallalkoholate wie z.B. Natriummethylat. Als inerte Lösungsmittel eignen sich beispielsweise die

entsprechenden niederen Alkohole, aromatische Kohlenwasserstoffe wie Toluol oder Xylol, oder Mischungen solcher Lösungsmittel. Bei der Umstzung fällt die Verbindung der Formel X in Form ihres Alkalimetallsalzes an und kann bei der Aufarbeitung durch Ansäuern des Reaktionsgemisches in Freiheit gesetzt werden.

Die für die Verfahrenvariante a') benötigten Ausgangsverbindungen der Formel VII können auf an sich bekannte Weise erhalten werden ausgehend von Phenylglycinverbindungen der Formel XI

(siehe Formel XI)

worin R_3 und R_4 obige Bedeutung besitzen, und welche durch Umsetzung der entsprechenden Aniline mit Chloressigsäure erhalten werden können, und o-Chlorbenzoesäuren der Formel XII

(siehe Formel XII)

worin R_3 und R_4 obige Bedeutung besitzen. Die Alkalimetallsalze, insbesondere Kaliumsalze, der Säuren der Formel XI werden mit Alkalimetallsalzen, insbesondere Kaliumsal-

zen, der Säuren der Formel XII bei erhöhter Temperatur, beispielsweise Temperaturen zwischen 100 und 150 oC, in Gegenwart einer anorganischen Base, beispielsweise Kaliumcarbonat, und eines Kupferkatalysators, beispielsweise Kupferpulver, in einem polaren Lösungsmittel, vorzugsweise Wasser oder einer Mischung aus Wasser und einem mit Wasser mischbaren organischen Lösungsmittel, zu Verbindungen der Formel XIII

(siehe Formel XIII)

worin R_3, R_4, R_5 und R_6 obige Bedeutung besitzen, umgesetzt, und diese dann in an sich bekannter Weise zu Verbindungen der Formel VII verestert, beispielsweise durch Umsetzung mit einem Alkohol $R_{12}OH$ in Gegenwart von Schwefelsäure bei erhöhter Temperatur, beispielsweise Siedetemperatur des Reaktionsgemisches.

Die vorstehend beschriebene Verfahrensvariante a') ist insbesondere zur Herstellung solcher Verbindungen der Formel Vb, worin R_3 und R_4 für Wasserstoff oder für solche Substituenten stehen, welche nicht zu einer Umsetzung mit Phenylglycin befähigt sind. Falls die Verbindung der Formel XIII weitere zur Umsetzung mit Phenylglycin befähigte Substituenten enthält, können bei dieser Umsetzung neben der Verbindung der Formel XIII auch mehrfach substituierte Nebenprodukte in dem Reaktionsgemisch entstehen. Das gewünschte Reaktionsprodukt kann auf chromatographischem Wege von allfälligen Nebenprodukten abgetrennt werden.

Die Umsetzung von Verbindungen der Formel VIII mit Verbindungen der Formel IX gemäß Verfahrensvariante b') kann auf an sich bekannte Weise erfolgen. Zweckmäßigerweise werden die Verbindungen der Formel VIII in Form ihrer Alkalimetallsalze, beispielsweise ihrer Natrium- oder Lithiumsalze, mit Verbindungen der Formel IX in einem unter den Reaktionsbedingungen inerten Lösungsmittel bei Temperaturen zwischen ca. 100 und 170 oC umgesetzt. Als Lösungsmittel eignen sich in dem angegebenen Temperaturbereich siedende inerte organische Lösungsmittel, vorzugsweise Dimethylformamid. Es ist zweckmäßig, die Reaktion in Gegenwart eines Kupferkatalysators, beispielsweise Kupferpulver oder Kupfer-I oder Kupfer-II-Halogeniden, durchzuführen. Die Alkalimetallsalze der Verbindungen der Formel VIII können auf an sich bekannte Weise durch Umsetzen mit einer starken Base, beispielsweise einem Alkalimetallalkoholat oder -hydrid oder -hydroxid, gewünschtenfalls in situ hergestellt werden.

Die für die Verfahrensvariante b') benötigten Ausgangsverbindungen der Formel VIII können auf an sich bekannte Weise ausgehend von Anthranilsäureestern der Formel XIV

(siehe Formel XIV)

worin R_3 und R_4 obige Bedeutung besitzen und R_{13} niederes Alkyl bedeutet, hergestellt werden, indem man diese zunächst mit Chloressigsäure oder einem Chloressigsäureniederalkylester in an sich bekannter Weise zu Verbindungen der Formel XV

(siehe Formel XV)

worin R_3, R_4 und R_{13} obige Bedeutung besitzen und R_{14} Wasserstoff oder niederes Alkyl bedeutet, umsetzt, falls R_{14} Wasserstoff ist, diese Säure in an sich bekannter Weise mit einem Alkohol $R_{12}OH$, worin R_{12} obige Bedeutung besitzt, verestert, und die erhaltenen Diester in an sich bekannter Weise zu Verbindungen der Formel XVI

(siehe Formel XVI)

worin R_3, R_4 und R_{12} obige Bedeutung besitzen, cyclisiert, welche dann durch Verätherung der Hydroxygruppe auf an sich bekannte Weise in Verbindungen der Formel VIII überführt werden. Die Cyclisierung der Ester der Formel XV kann beispielsweise unter den für die Cyclisierung der Ester der Formel VII vorstehend beschriebenen Bedingungen erfolgen.

Die Verfahrensvariante b') eignet sich insbesondere zur Herstellung solcher Verbindungen der Formel Vb, worin R_5 und R_6 für Wasserstoff oder für solche Substituenten stehen, welche nicht zu einer Umsetzung mit den Alkalimetallsalzen der Verbindungen der Formel XIII befähigt sind.

Die Verbindungen der Formel I und ihre pharmakologisch akzeptablen Säureadditionssalze zeichnen sich durch interessante pharmakologische Eigenschaften aus und zeigen insbesondere herzrhythmisierende Wirkungen. Die neune Verbindungen zeichnen sich aus durch eine gute Wirksamkeit und hohe physiologische Verträglichkeit. So zeigen die neuen Verbindungen schon in geringen Dosen eine befriedigende antiarrhythmische Wirkung. Darüber hinaus ist eine unerwünschte negative Beeinflussung des Kontraktionsvermögens des Herzens äußerst gering. Das heißt, die Verbindungen weisen ein besonders günstiges Verhältnis von antiarrhythmischen, bzw. die Refraktärzeit des Herzens verlängernden Wirkungen zu negativ inotropen Nebenwirkungen auf und besitzen eine große therapeutische Breite.

Die zu verwendenden Dosen variieren naturgemäß je nach Art der verwendeten Substanz, der Applikationsart und des zu behandelnden Zustandes. Im allgemeinen werden jedoch befriedigende Ergebnisse in Tierversuchen mit Dosen von 0,1 bis 100 mg/kg Körpergewicht erhalten.

Die antiarrhythmischen Wirkungen der Verbindungen lassen sich in pharmakologischen Standardtestmethoden nachweisen.

Ein günstiges Verhältnis von die funktionelle Refraktärzeit verlängernder Wirkung (FRZ) zu die Kontraktionskraft vermindernder Wirkung (Kraft) der Verbindungen läßt sich zum Beispiel am isolierten linken Vorhof von weiblichen Meerschweinchen von 300 bis 400 g Körpergewicht gemäß der Doppelreizmethode von Govier [J.Pharmakol. Exp. Ther. 148 (1965) 100-105] zeigen. In der nachfolgenden Tabelle sind angegeben diejenige Konzentration in µmol/l, bei der es 18 Minuten nach Applikation zu einer Verlängerung der funktionellen Refraktärzeit auf 125 % kommt und diejenige Konzentration, bei der es zu einer Verminderung der Kontraktionskraft auf 75 % des Ausgangswertes kommt, und außerdem der Quotient aus diesen Konzentrationen, welcher ein Indiz für die therapeutische Breite der Verbindungen darstellt.

Beispiel Nr.	isolierter Meerschweinchen-Vorhof Kraft [µmol/l]	FRZ [µmol/l]	Kraft / FRZ
4	4,2	3,0	1,4
3	6,2	2,8	2,2
21	1,8	0,73	2,5

Ebenso zeigen die Verbindungen in Ratten in der Versuchsmethode nach Raschak (Arzneimittelforsch. 25 (1975) 639-641) eine hemmende Wirkung gegenüber den durch Aconitin-Infusion induzierten Herzrhythmusstörungen.

Aufgrund der vorstehend beschriebenen Wirkungen eignen sich die Verbindungen der Formel I und ihre pharmakologisch akzeptablen Säureadditionssalze als Arzneimittel zur Behandlung von Herzrhythmusstörungen.

Ferner zeigen die Substanzen der Formel I auch antithrombotische Eigenschaften.

Als Heilmittel können die Verbindungen der Formel I und ihre physiologisch verträglichen Säureadditionssalze mit üblichen pharmazeutischen Hilfsstoffen in galenischen Zubereitungen wie z.B. Tabletten, Kapseln, Suppositorien oder Lösungen enthalten sein. Diese galenischen Zubereitungen können nach an sich bekannten Methoden hergestellt werden unter Verwendung üblicher fester Trägerstoffe wie z.B. Milchzucker, Stärke oder Talkum oder flüssiger Verdünnungsmittel wie z.B. Wasser, fetten Ölen oder flüssigen Paraffinen.

Die nachfolgenden Beispiele sollen die Herstellung der neuen Verbindungen der Formel I näher erläutern jedoch den Umfang der Erfindung in keiner Weise beschränken.

Beispiel 1:

2-[3-(N,N-Diäthylamino)propylaminocarbonyl]-3-acetoxy-1-phenylindol.

A) 475 g Chloressigsäure (5 Mol) werden mit 930 g Anilin (10 Mol) in 2 l Wasser 1,5 Stunden lang auf 100 °C erhitzt. Nach dem Abkühlen wird das gebildete N-Phenylglycin abgesaugt und mit Wasser gewaschen. Ausbeute 468 g (= 62 % bezogen auf Chloressigsäure).

B) 468 g N-Phenylglycin werden unter Erwärmung in 1,3 l Methanol gelöst. Die Lösung wird unter Kühlung mit einer Lösung von 205 g Kaliumhydroxyd in 450 ml Methanol versetzt. Nach dem Abkühlen wird das ausgefallene Kaliumsalz des N-Phenylglycins abgesaugt. Ausbeute 392 g = 67 %.

C) 468 g o-Chlorbenzoesäure werden unter Erwärmung in 1,5 l Isopropanol gelöst. Die Lösung wird unter Kühlung mit einer Lösung von 198 g Kaliumhydroxyd in 200 ml Methanol versetzt. Nach dem Abkühlen wird das ausgefallene Kaliumsalz der o-Chlorbenzoesäure abgesaugt. Ausbeute 394 g = 67,4 %.

D) 750 g des Kaliumsalzes des N-Phenylglycins werden mit 808 g des Kaliumsalzes der o-Chlorbenzoesäure, 268 g Kaliumcarbonat und 1,5 g Kupfer-Pulver in 385 ml Wasser 5 Stunden lang auf 120 bis 125 °C (Innentemperatur) erhitzt. Nach dem Lösen des Reaktionsgemisches in Wasser wird die Lösung mit Salzsäure angesäuert und die ausgefallene N-Diphenylglycin-o-carbonsäure abgesaugt. Ausbeute 675 g = 62,7 %.

E) 675 g N-Diphenylglycin-o-carbonsäure werden mit 2,5 l Methanol und 500 ml Schwefelsäure 5 Stunden lang zum Sieden erhitzt. Das Methanol wird teilweise abgedampft, die Reaktionsmischung anschließend in Wasser gegossen und mit Methylenchlorid extrahiert. Die Methylenchlo-

ridphase wird mit Sodalösung ausgeschüttelt, getrocknet und eingedampft, wobei der rohe N-Diphenylglycin-o-carbonsäuredimethylester als Rückstand erhalten wird. Ausbeute 614 g Rohprodukt = 82,4 %.

F) 47,1 g Natrium werden in 500 ml Methanol gelöst und die Lösung mit 500 ml Toluol versetzt. Das Gemisch wird zum Sieden erhitzt und unter schwachem Rückfluß mit einer Lösung von 614 g N-Diphenylglycin-o-carbonsäuredimethylester in 1,5 l Toluol versetzt. Nach weiteren 30 Minuten Siedens wird die Reaktionsmischung abgekühlt und in 1 l Wasser gegeben und mit 250 ml Salzsäure angesäuert. Der ausgefallene N-Phenylindoxylsäuremethylester wird abgesaugt. Ausbeute 464 g = 84,8 %.

G) 140 g N-Phenylindoxylsäuremethylester werden in 600 ml Aceton mit 69 ml Dimethylsulfat und 71 g Kaliumcarbonat während 4 Stunden unter Rühren zum Sieden erhitzt. Die Reaktionsmischung wird in Wasser gegossen und der gebildete N-Phenyl-3-methoxyindol-2-carbonsäuremethylester wird abgesaugt und in 450 ml Methanol aufgelöst. Die Lösung wird mit einer Lösung von 42 g Natriumhydroxyd in 50 ml Wasser versetzt und 30 Minuten lang zum Sieden erhitzt. Das Reaktionsgemisch wird in Wasser gelöst, die wäßrige Lösung wird mit Salzsäure angesäuert und die ausgefallene N-Phenyl-3-methoxyindol-2-carbonsäure wird abgesaugt. Ausbeute 127 = 90,7 %.

H) 92 g N-Phenyl-3-methoxyindol-2-carbonsäure werden in 920 ml Äther und 30,3 g Pyridin gelöst. Die Lösung wird unter Eiskühlung in eine Lösung von 28,3 ml Thionylchlorid in 160 ml Äther unter Rühren eingetropft. Die Mischung wird 1 Stunde lang bei Raumtemperatur gerührt und die ausgefallenen Pyridinsalze werden abgesaugt.

Die erhaltene ätherische Lösung des N-Phenyl-3-methoxyindol-2-carbonsäurechlorids wird unter Eiskühlung zu einer Lösung von 550 g 1-Amino-3-diäthylami-

nopropan und 40 g Triäthylamin in 70 ml Methylenchlorid getropft. Das Reaktionsgemisch wird 1 Stunde bei Raumtemperatur gerührt und anschließend mit verdünnter Salzsäure extrahiert. Der Salzsäureextrakt wird durch Zugeben von Natronlauge alkalisch gemacht und mit Äther extrahiert. Die Ätherlösung wird mit Wasser gewaschen, über Natriumsulfat getrocknet und eingedampft. Es verbleibt 2-[3-(N,N-Diäthylamino)propylaminocarbonyl]-3-methoxy-1-phenylindol als ölige Base. Diese wird in Isopropanol gelöst und in ihr Hydrochlorid überführt. Schmelzpunkt 135-137 oC.

I) 2,1 g 2-[3-(N,N-Diäthylamino)propylaminocarbonyl]-3-methoxy-1-phenylindol-hydrochlorid werden in 5 ml Methanol gelöst und mit 2,5 ml konzentrierter Salzsäure versetzt. Das Reaktionsgemisch wird 3 Stunden lang unter Rückfluß gekocht und anschließend im Vakuum eingedampft. Man erhält 1,66 g (82 % der Theorie) 2-[3-(N,N-Diäthylamino)propylaminocarbonyl]-3-hydroxy-1-phenylindol-hydrochlorid als ölige Substanz. IR: 1647 cm^{-1} (CO Amid).

J) 1,66 g 2-[3-(N,N-Diäthylamino)propylaminocarbonyl]-3-hydroxy-1-phenylindol-hydrochlorid werden in 25 ml Dichlormethan gelöst und nacheinander unter kräftigem Rühren mit 0,6 ml Triäthylamin und 0,3 ml Acetylchlorid versetzt. Die Reaktionsmischung wird 30 Minuten lang unter Rückfluß gekocht. Nach Abkühlen wird die Mischung mit wenig gesättigter Kochsalzlösung gewaschen, die organische Phase über Natriumsulfat getrocknet und im Vakuum eingedampft. Nach Umkristallisieren aus Isopropanol erhält man 1,00 g (57 % der Theorie) 2-[3-(N,N-Diäthylamino)-propylaminocarbonyl]-3-acetoxy-1-phenylindol-hydrochlorid. Fp.: 174-176 oC.
IR-Spektrum: 1771 cm^{-1}, 1663 cm^{-1}

Beispiel 2:

2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-benzyloxy-1-phenylindol.

A) 112 g N-Phenylindoxylessigsäuremethylester (hergestellt entsprechend Beispiel 1, A) bis F) werden in 600 ml Dimethylformamid mit Natriummethylat (hergestellt aus 16,6 g Natriumhydroxyd und Methanol) und 54 ml Benzylbromid 2 Stunden unter Rückfluß erhitzt. Anschließend wird ein Teil des Dimethylformamids abdestilliert, die verbleibende Lösung mit Wasser versetzt und der ausgefallene N-Phenyl-3-benzyloxyindol-2-carbonsäuremethylester abgesaugt und zur Verseifung mit 19 g Natriumhydroxyd in 600 ml 50 %-igem Äthanol 2 Stunden am Rückfluß erhitzt. Das Reaktionsgemisch wird in Wasser gelöst, die wäßrige Phase wird mit Salzsäure angesäuert und die ausgefallene N-Phenyl-3-benzyloxyindol-2-carbonsäure wird abgesaugt.

B) 10,5 g N-Phenyl-3-benzyloxyindol-2-carbonsäure werden mit 4,5 g 2-Chlor-N-Pyridiniumjodid, 4,2 ml Triäthylamin und 2,5 g 1-Amino-2-hydroxy-3-diäthylaminopropan in 45 ml Methylenchlorid bei Raumtemperatur umgesetzt. Nach 14 Stunden wird das Reaktionsgemisch mit gesättigter Natriumchloridlösung und mit 10 %-iger Natriumcarbonatlösung gewaschen, über Natriumsulfat getrocknet, filtriert und eingedampft. Der Rückstand wird in verdünnter Salzsäure/Äther gelöst, und die Ätherphase abgetrennt. Die wäßrige Phase wird alkalisch gestellt und mit Äther extrahiert. Der Ätherextrakt wird mit Wasser gewaschen, über Natriumsulfat getrocknet und eingedampft. Das als Rückstand verbleibende rohe 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-benzyloxy-1-phenylindol wird aus Isopropanol/Äther umkristallisiert. Schmelzpunkt 80-81 °C.
IR-Spektrum: 1647 cm^{-1}

Beispiel 3:

2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-pivaloyloxy-1-phenylindol.

A) Die aus Umsetzung von 92 g N-Phenyl-3-methoxyindol-2-carbonsäure mit Thionylchlorid und Pyridin in Äther gemäß Beispiel 1H erhaltene ätherische Lösung von N-Phenyl-3-methoxy-indol-2-carbonsäurechlorid wird unter Eiskühlung zu einer Lösung von 57,9 g 1-Amino-2-hydroxy-3-diäthylaminopropan und 40 g Triäthylamin in 70 ml Methylenchlorid getropft. Das Reaktionsgemisch wird 1 Stunde bei Raumtemperatur gerührt und anschließend wie in Beispiel 1H beschrieben aufgearbeitet. Es werden 110 g 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-methoxy-1-phenylindol-hydrochlorid erhalten, Schmelzpunkt 148-150 °C.

B) 15 g 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-methoxy-1-phenylindol-hydrochlorid werden mit 15 ml Methanol und 15 ml konzentrierter Salzsäure 3 Stunden lang unter Rückfluß gekocht. Anschließend wird das Reaktionsgemisch im Vakuum eingedampft. Das als Rückstand verbleibende 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-hydroxy-1-phenylindolhydrochlorid besitzt nach Umkristallisieren aus Isopropanol einen Schmelzpunkt von 166-168 °C.

C) 12,6 g 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-hydroxy-1-phenylindol-hydrochlorid (0,03 Mol) werden mit 150 ml Methylenchlorid, 4,2 ml Triäthylamin (0,03 Mol) und 3,9 ml Pivaloylchlorid (0,03 Mol) versetzt und das Reaktionsgemisch wird 3 Stunden bei Raumtemperatur stehengelassen. Anschließend wird mit gesättigter Kochsalzlösung gewaschen und über Natriumsulfat getrocknet und filtriert. Die Lösung wird sodann eingedampft, der Rückstand in Methylenchlorid gelöst und durch Niederdruckchromatographie über eine Kieselgelsäure gereinigt. Als Elutionsmittel wird zunächst Methylenchlorid und anschließend 10 % Methanol enthaltendes Methylenchlorid verwendet. Das nach Eindampfen des Eluates als Rückstand erhaltene 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-pivaloyloxy-1-phe-

nylindol-hydrochlorid wird anschließend aus Isopropanol umkristallisiert, Schmelzpunkt 157-159 °C.
IR-Spektrum: 1758 cm^{-1}, 1661 cm^{-1}

Beispiel 4:
2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-benzoyloxy-1-phenylindol.

2,1 g 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-hydroxy-1-phenylindol-hydrochlorid (0,005 Mol, hergestellt analog Beispiel 3 B) werden in 25 ml trockenem Methylenchlorid mit 0,3 g (0,01 Mol) Natriumhydrid (80 %-ig) versetzt. Nach 30 Minuten werden in der Kälte 1,5 ml Benzoylchlorid (0,012 Mol) zugesetzt und das Reaktionsgemisch 16 Stunden bei Raumtemperatur stehengelassen. Anschließend wird die Lösung filtriert, mit gesättigter Kochsalzlösung gewaschen, über Natriumsulfat getrocknet und eingedampft. Das als Rückstand erhaltene Rohprodukt besteht aus einem Gemisch der Hydrochloride des 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-benzoyloxy-1-phenylindol und des 2-[3-(N,N-Diäthylamino)-2-benzoyloxypropylaminocarbonyl]-3-benzoyloxy-1-phenylindol. Dieses Rohprodukt wird in Äthylacetat gelöst und die Lösung mit Diäthyläther versetzt, wobei das Hydrochlorid des 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-benzoyloxy-1-phenylindol kristallin erhalten wird. Nach Umkristallisation aus Äthylacetat/Diäthyläther zeigt es einen Schmelzpunkt von 130-133 °C
IR-Spektrum: 1735 cm^{-1}, 1654 cm^{-1}.

Beispiel 5:
2-[3-(N,N-Diäthylamino)-2-acetoxypropylaminocarbonyl]-3-acetoxy-1-phenylindol.

10,5 g 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-hydroxy-1-phenylindol-hydrochlorid (0,025 Mol) werden mit 100 ml Methylenchlorid und 7,0 ml Triäthylamin (0,05 Mol) versetzt. Anschließend werden der Reaktionslö-

sung 3,6 ml Acetylchlorid (0,05 Mol) zugefügt und das Reaktionsgemisch 18 Stunden bei Raumtemperatur stehengelassen. Dann wird die Lösung mit gesättigter Kochsalzlösung gewaschen, über Natriumsulfat getrocknet, filtriert und eingedampft. Das als Rückstand verbleibende Rohprodukt wird durch Niederdruckchromatographie wie in Beispiel 3 beschrieben gereinigt. Man erhält das 2-[3-(N,N-Diäthylamino)-2-acetoxypropylaminocarbonyl]-3-acetoxy-1-phenylindol-hydrochlorid als öliges Produkt.
IR-Spektrum: 1778 cm^{-1}, 1741 cm^{-1}, 1663 cm^{-1}.

Beispiel 6:

2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-methoxycarbonyläthylcarbonyloxy-1-phenylindol.

2,1 g 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-hydroxy-1-phenylindol-hydrochlorid (0,005 Mol) werden in 25 ml Methylenchlorid mit 0,7 ml Triäthylamin (0,005 Mol) und 0,6 ml Bernsteinsäuremethylesterchlorid versetzt und das Reaktionsgemisch 1 Stunde bei Raumtemperatur gerührt. Anschließend wird die Lösung mit gesättigter Kochsalzlösung gewaschen, über Natriumsulfat getrocknet, filtriert und eingedampft. Der Rückstand wird durch Niederdruckchromatographie unter Verwendung von Methylenchlorid als Elutionsmittel wie in Beispiel 3 beschrieben gereinigt. Man erhält das 2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-methoxycarbonyläthylcarbonyloxy-1-phenylindol-hydrochlorid als öliges Produkt.
IR-Spektrum: 1768 cm^{-1}, 1734 cm^{-1}, 1654 cm^{-1}.

Nach den in den Beispielen 1 bis 6 beschriebenen Verfahren können auch die in der folgenden Tabelle aufgeführten Verbindungen der Formel I durch Acylierung entsprechender Verbindungen der Formel II bzw. Amidbildung aus Verbindungen der Formel Va hergestellt werden.

Beispiel Nr.	R_3	R_4	R_5	R_6	R_2	Z	R_7	R_8	R_1	Bemerkungen Fp in °C, HCl = Hydrochlorid IR-banden in cm^{-1}
7	H	H	H	H	H	$CH_2-CH_2-CH_2$	C_2H_5	C_2H_5	-CO-	HCl, Fp.190-192 IR: 1736, 1662
8	H	H	4-Cl	H	H	CH_2-CH_2	CH_3	CH_3	$-CO-C(CH_3)_3$	HCl, Fp.215-217 IR: 1761, 1663
9	H	H	4-Cl	H	H	$CH_2-CH_2-CH_2$	CH_3	CH_3	$-CO-C(CH_3)_3$	HCl, ölig IR: 1751, 1653
10	H	H	2,3-di-CH_3		H	CH_2-CH_2	CH_3	CH_3	$-CO-C(CH_3)_3$	HCl, Fp.118-120 IR: 1752, 1663
11	5-Br	H	H	H	H	CH_2-CH_2	CH_3	CH_3	$-CO-C(CH_3)_3$	HCl, Fp.210-212 IR: 1758, 1652
12	H	H	4-Cl	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	$-CO-C(CH_3)_3$	HCl, ölig IR: 1752, 1663
13	H	H	4-CH_3O	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	$-CO-C(CH_3)_3$	HCl, ölig IR: 1757, 1653
14	H	H	4-F	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	$-CO-C(CH_3)_3$	HCl, Fp.183-185 IR: 1756, 1663
15	H	H	4-F	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	-CO-	HCl, Fp.186-188 IR: 1741, 1662
16	H	H	4-Cl	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	-CO-	HCl, Fp.190-194 IR: 1743, 1658
17	H	H	H	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	-CO--NO_2	HCl, ölig IR: 1749, 1653
18	H	H	H	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	-CO--CH_3	HCl, ölig IR: 1734, 1653
19	H	H	H	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	-CO--OCH_3	HCl, ölig IR: 1734, 1654
20	H	H	H	H	H	$CH_2-CH(OH)-CH_2$	C_2H_5	C_2H_5	$-CO-n-C_{11}H_{23}$	HCl, ölig IR: 1765, 1653
21	H	H	H	H	H	$CH_2-CH(O-CO-$$)-CH_2$	C_2H_5	C_2H_5	-CO-	HCl, Fp.173-175 IR: 1744, 1725, 1669

Beispiel Nr.	R_3	R_4	R_5	R_6	R_2	Z	R_7	R_8	R_1	Bemerkungen Fp in °C, HCl = Hydrochlorid IR-banden in cm^{-1}
22	H	H	H	H	H	CH_2-CH(O-CO-C$_6$H$_4$-CH_3)-CH_2	C_2H_5	C_2H_5	-CO-C$_6$H$_4$-CH_3	HCl, ölig IR: 1744, 1717, 1669
23	H	H	4-Cl	H	H	CH_2-CH(O-CO-C$_6$H$_5$)-CH_2	C_2H_5	C_2H_5	-CO-C$_6$H$_5$	HCl, Fp.127-129 IR: 1741, 1720, 1669
24	H	H	H	H	H	CH_2-CH(OH)-CH_2	C_2H_5	C_2H_5	-C$_6$H$_4$-CH_3	HCl, ölig IR: 1647
25	H	H	H	H	H	CH_2-CH(OH)-CH_2	C_2H_5	C_2H_5	-C$_6$H$_4$-Cl	Base, öl IR: 1658
26	H	H	H	H	H	CH_2-CH(OH)-CH_2	C_2H_5	C_2H_5	-C$_6$H$_4$-NO_2	Base, öl IR: 1647
27	H	H	H	H	H	CH_2-CH(OH)-CH_2	C_2H_5	C_2H_5	-C$_6$H$_4$(Cl)	Base, öl IR: 1647

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Beispiel I: Tabletten

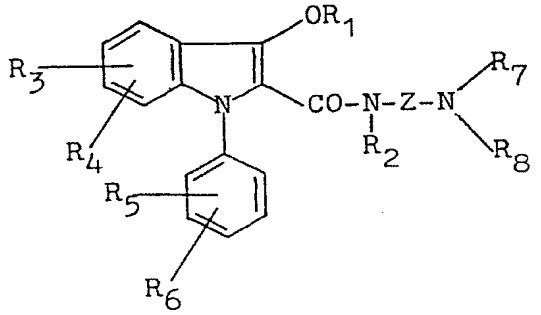
Man stellt Tabletten in folgender Zusammensetzung pro Tablette her:

2-[3-(N,N-Diäthylamino)-2-hydroxypropylaminocarbonyl]-3-pivalo-yloxy-1-phenylindol-hydrochlorid	15 mg
Maisstärke	60 mg
Milchzucker	140 mg
Gelatine (als 10 %-ige Lösung)	6 mg

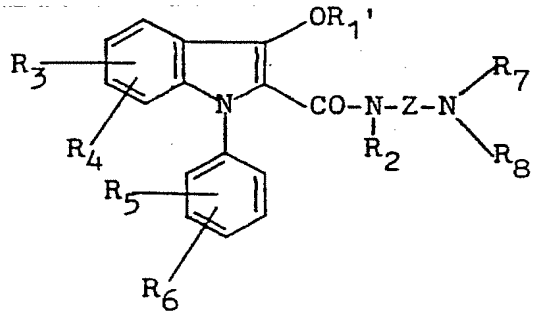
Der Wirkstoff, die Maisstärke und der Milchzucker werden mit der 10 %-igen Gelatine-Lösung eingedickt. Die Paste wird zerkleinert und das entstandene Granulat wird auf ein geeignetes Blech gebracht und bei 45 °C getrocknet. Das getrocknete Granulat wird durch eine Zerkleinerungsmaschine geleitet und in einem Mixer mit weiteren folgenden Hilfsstoffen vermischt:

Talkum	5 mg
Magnesiumstearat	5 mg
Maisstärke	9 mg

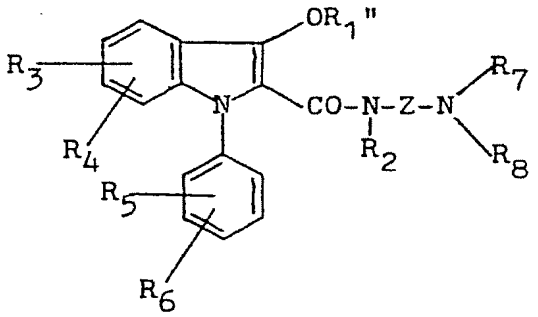
und sodann zu Tabletten von 240 mg verpreßt.



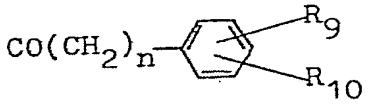
I



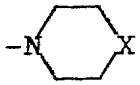
Ia



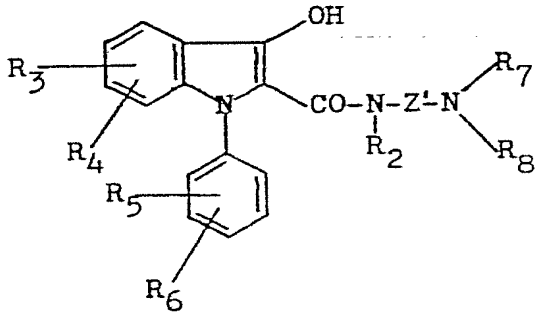
Ib



a

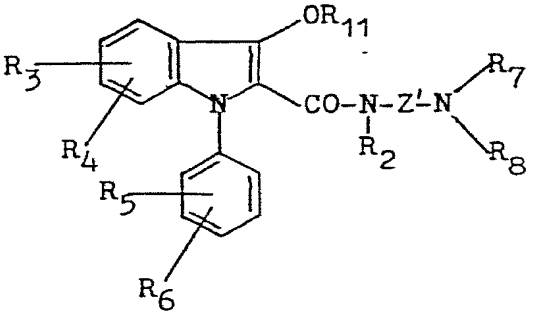


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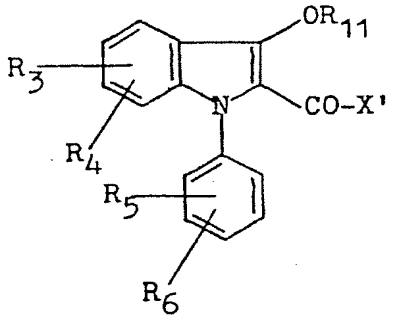


II

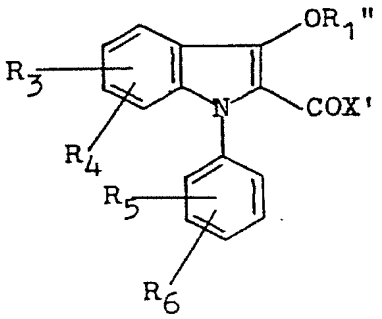
$R_1'-X$ III



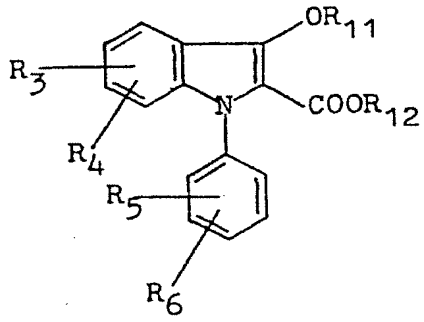
IV



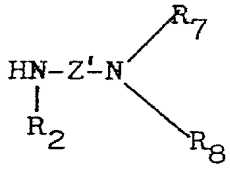
V



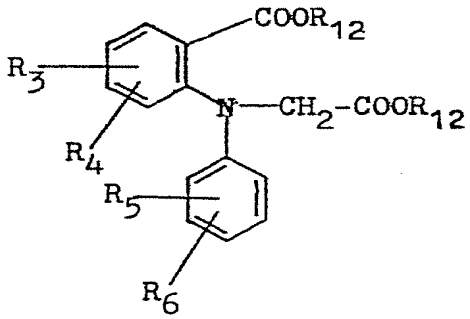
Va



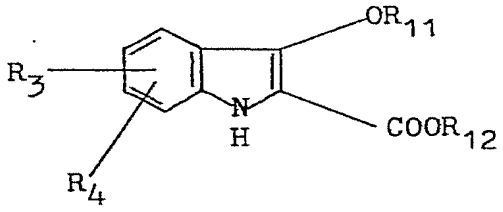
Vb



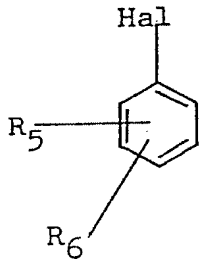
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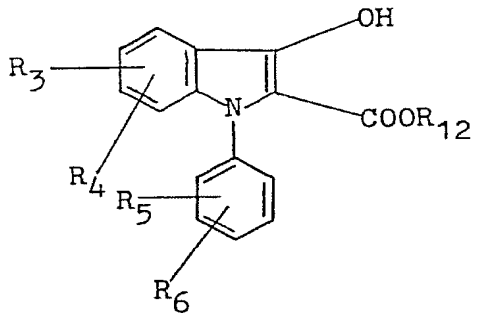
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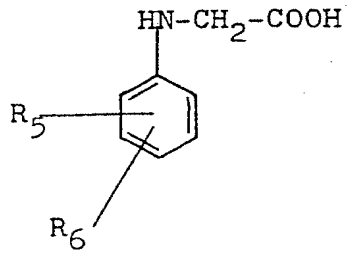
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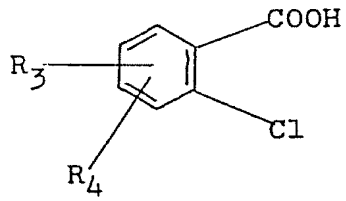
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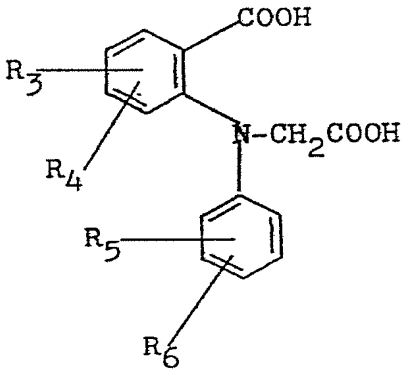
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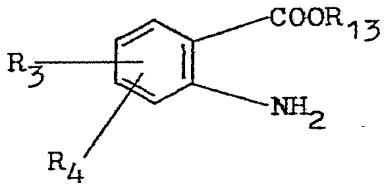
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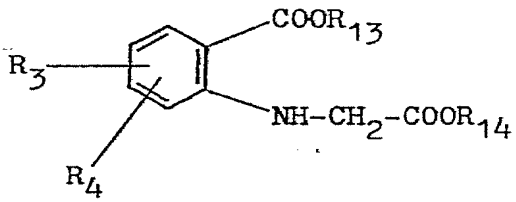
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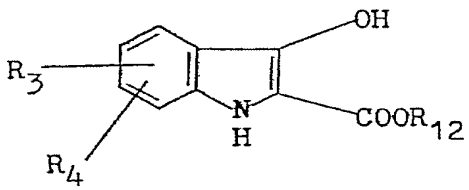
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XIV



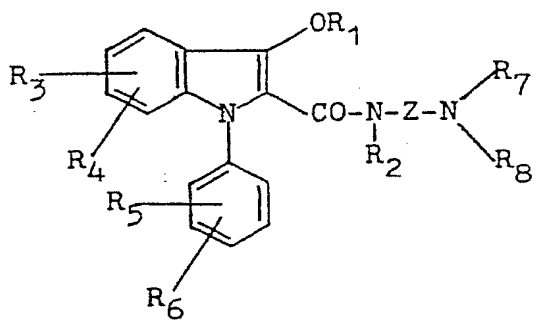
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XVI

Patentansprüche

1. 1-Phenyl-2-aminocarbonylindol-Verbindungen der allgemeinen Formel I

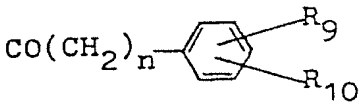


I

worin

R_1 eine Alkanoylgruppe mit 2 bis 12 Kohlenstoffatomen bedeutet, welche gegebenenfalls substituiert sein kann durch eine Carboxyl- oder niedere Alkoxycarbonylgruppe oder niederes Alkoxy oder Benzyloxy, oder

R_1 eine Gruppe a



a

bedeutet, worin n 0, 1, 2 oder 3 ist und R_9 und R_{10} unabhängig voneinander Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy oder, falls sie an 2 benachbarte Kohlenstoffatome gebunden sind, auch gemeinsam Methylendioxy darstellen, oder, falls n 0 ist und R_9 Wasserstoff darstellt, R_{10} auch Nitro oder Trifluormethyl bedeutet, oder

R_1 Benzyl, welches gegebenenfalls substituiert sein kann durch 1 bis 2 Substituenten aus der Gruppe niederes Alkyl, niederes Alkoxy, Nitro und Halogen, bedeutet,

R_2 Wasserstoff oder niederes Alkyl bedeutet,

R_3 Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy bedeutet.

R_4 Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy bedeutet,

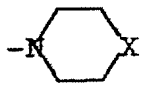
R_5 Wasserstoff, niederes Alkyl, Halogen oder niederes Alkoxy bedeutet,

R_6 Wasserstoff, niederes Alkyl, niederes Alkoxy, Halogen oder, falls R_5 Wasserstoff ist, auch Nitro oder Trifluormethyl bedeutet,

R_7 Wasserstoff oder niederes Alkyl bedeutet,

R_8 Wasserstoff oder niederes Alkyl bedeutet, oder

R_7 und R_8 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe b bilden,



b

worin

X für eine Bindung, $-CH_2-$, $-C_2H_4-$, O oder S steht,

Z eine Alkylenkette mit 2 bis 5 Kohlenstoffatomen bedeutet, welche gegebenenfalls an einem nicht an Stickstoff gebundenen Kohlenstoff durch Hydroxy oder eine R'_1O-Gruppe, worin R'_1 die für R_1 angegebene Bedeutung mit Ausnahme von gegebenenfalls substituiertem Benzyl besitzt, substituiert ist,

sowie deren Säureadditionssalze.

2. 1-Phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 1, worin Z und R_1 bis R_6 die in Anspruch 1 angegebene Bedeutung besitzen, R_7 Wasserstoff oder niederes Alkyl bedeutet und R_8 Wasserstoff oder niederes Alkyl bedeutet.

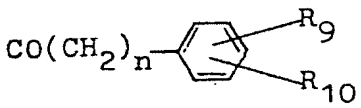
3. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 1, worin Z die in Anspruch 1 angegebene Bedeutung besitzt, R_1 die Acylgruppe R'_1 bedeutet, R_2 Wasserstoff bedeutet, R_3 Wasserstoff oder Halogen bedeutet, R_4 Wasserstoff oder Halogen bedeutet, R_5 Wasserstoff, Halogen oder niederes Alkyl bedeutet, R_6 Wasserstoff, Halogen oder niederes Alkyl bedeutet, R_7 Wasserstoff oder niederes Alkyl bedeutet und R_8 Wasserstoff oder niederes Alkyl bedeutet.

4. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 3, worin R_1 bis R_8 die in Anspruch 3 angegebene Bedeutung besitzen und Z eine Alkylenkette mit 2 bis 5 Kohlenstoffatomen, welche an einem nicht an Stickstoff gebundenen Kohlenstoff durch Hydroxy oder eine R'_1O-Gruppe substituiert ist, bedeutet.

5. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 4, worin R_1, R_7, R_8 und Z die in Anspruch 4 angegebene Bedeutung besitzen, und R_2 bis R_6 Wasserstoff bedeuten.

6. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 1, worin R_2 bis R_8 und Z die in Anspruch 1 angegebene Bedeutung besitzen und R_1 eine Alkanoylgruppe mit 2 bis 5 Kohlenstoffatomen bedeutet.

7. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 1, worin R_2 bis R_8 und Z die in Anspruch 1 angegebene Bedeutung besitzen und R_1 eine Gruppe a



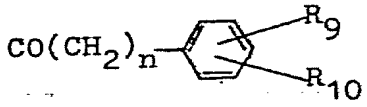
a

bedeutet, worin n 0 oder 1 ist und R_9 und R_{10} unabhängig voneinander Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy darstellen, oder, falls n 0 ist

und R_9 Wasserstoff darstellt, R_{10} auch Nitro oder Trifluormethyl bedeutet.

8. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 3, worin R_2 bis R_8 und Z die in Anspruch 3 angegebene Bedeutung besitzen und R_1 eine Alkanoylgruppe mit 2 bis 5 Kohlenstoffatomen bedeutet.

9. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 3, worin R_2 bis R_8 und Z die in Anspruch 3 angegebene Bedeutung besitzen und R_1 eine Gruppe a



a

bedeutet, worin n 0 oder 1 ist und R_9 und R_{10} unabhängig voneinander Wasserstoff, Halogen, niederes Alkyl oder niederes Alkoxy darstellen, oder, falls n 0 ist und R_9 Wasserstoff darstellt, R_{10} auch Nitro oder Trifluormethyl bedeutet.

10. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 1, worin R_2 bis R_6 Wasserstoff bedeuten, R_7 und R_8 Äthyl bedeuten, Z die 2-Hydroxypropylengruppe bedeutet und R_1 für Pivaloyl oder Benzoyl steht.

11. 3-Acyloxy-1-phenyl-2-aminocarbonylindol-Verbindungen gemäß Anspruch 1, worin R_2 bis R_6 Wasserstoff bedeuten, R_7 und R_8 Äthyl bedeuten, Z die 2-Hydroxypropylengruppe oder eine R'1 0-Propylengruppe bedeutet und R_1 für Acetyl, Propionyl, Isobutyryl, Pivaloyl, Dodecanoyl, Benzoyl, Chlorbenzoyl, Nitrobenzoyl, Methylbenzoyl, Methoxybenzoyl oder Phenylacetyl steht.

12. Arzneimittel enthaltend eine pharmakologisch wirksame Menge einer 1-Phenyl-2-aminocarbonylindol-Verbindung

gemäß Anspruch 1 und übliche Hilfs- und/oder Trägerstoffe.

Europäisches Patentamt

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EUROPÄISCHER RECHERCHENBERICHT

EP 84 10 1179

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl. ³)
D,A	FR-M- 1 527 (SESI) * Insgesamt *	1,2	C 07 D 209/42 A 61 K 31/405
A	FR-M- 5 723 (SESI) * Zusammenfassung *	1,2	
P,X	EP-A-0 071 935 (KALI CHEMIE PHARMA) * Ansprüche *	1,2	

RECHERCHIERTE SACHGEBIETE (Int. Cl. ³)

C 07 D 209/00

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Recherchenort	Abschlußdatum der Recherche	Prüfer
DEN HAAG	25-04-1984	MAISONNEUVE J.A.

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(54) Title: INDOLES AS INHIBITORS OF HIV REVERSE TRANSCRIPTASE

(57) Abstract

Novel indole compounds inhibit HIV reverse transcriptase, and are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

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TITLE OF THE INVENTION

INDOLES AS INHIBITORS OF HIV REVERSE TRANSCRIPTASE

This application is a continuation-in-part of U.S. Serial Number 07/832,260 filed February 7, 1992, which itself is a continuation-in-part of U.S. Serial Number 07/756,013 filed September 6, 1991.

The present invention is concerned with compounds which inhibit the reverse transcriptase encoded by human immunodeficiency virus (HIV) or pharmaceutically acceptable salts thereof and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of the resulting acquired immune deficiency syndrome (AIDS). It also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the treatment of AIDS and viral infection by HIV.

BACKGROUND OF THE INVENTION

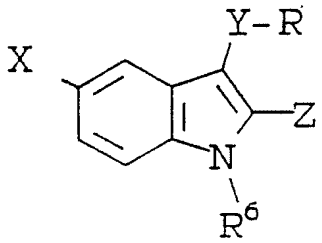
A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is reverse transcription of the RNA genome by a virally encoded reverse transcriptase to generate DNA copies of HIV sequences, a required step in viral replication. It is known that some compounds are reverse transcriptase inhibitors and are effective agents in the treatment of AIDS and similar diseases, e.g., azidothymidine or AZT.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature 329, 351 (1987)].

The compounds of this invention are inhibitors of HIV reverse transcriptase. Furthermore, the compounds of the present invention do not require bioactivation to be effective.

BRIEF DESCRIPTION OF THE INVENTION

Novel compounds of formula A:



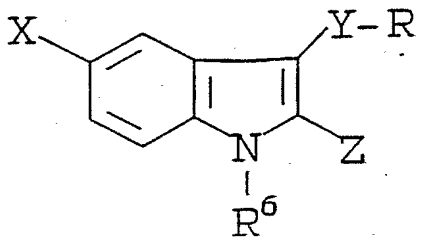
A

as herein defined, are disclosed. These compounds are useful in the inhibition of HIV reverse transcriptase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the compounds of formula A described below, combinations thereof, or pharmaceutically acceptable salts or esters thereof, in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired

immune deficiency syndrome (AIDS). The compounds of this invention are those with structural formula A:



A

wherein

X is -H, -Cl, -F, -Br, $-NO_2$, -CN, or $-OR^2$;

Y is $-S(O)_n-$, $-CR^2R^2-$ or -O-, wherein n is zero, 1 or 2;

R is
1) hydrogen,
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl,
 b) $-C_{1-5}$alkoxy,
 c) -OH, or
 d) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH, or
 iv) halogen,
3) aryl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 i) -OH or
 ii) $-C_{1-5}$alkoxy,

b) $-C_{1-5}$alkoxy,
c) -OH, or
d) halogen, or

4) heterocycle, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) $-C_{1-5}$alkoxy,
b) $-C_{1-5}$alkoxy, or
c) -OH;

Z is 1) $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein W is O, S, -N-CN or $-N-OR^1$,

2) $-\overset{\overset{O}{\|}}{C}-OR^1$,

3) $-\overset{\overset{O}{\|}}{C}-R^1$,

4) $-CR^2R^2-\underset{\underset{(O)_n}{|}}{S}-R^1$,

wherein n is defined above,

5) $-CR^2R^2NHR^4$,

6) $-CR^2R^2-\overset{\overset{O}{\|}}{C}-R^5$,

7) $-C_{1-3}$alkyl, unsubstituted or substituted with one or more of:
 a) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH or
 iv) halogen, or
 b) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or
8) -CN;

R^1 is
1) hydrogen,
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl,
 b) $-C_{1-5}$alkoxy,
 c) -OH,
 d) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or
 e) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or

3) aryl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 i) -OH or
 ii) $-C_{1-5}$alkoxy,
 b) $-C_{1-5}$alkoxy,
 c) -OH,
 d) halogen,
 e) -CN,
 f) $-NO_2$, or
 g) $-NR^2R^2$; or
4) heterocycle, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 i) -OH or
 ii) $-C_{1-5}$alkoxy,
 b) $-C_{1-5}$alkoxy, or
 c) -OH;

R^2 is hydrogen or C_{1-3}alkyl;

R^3 is
1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl,
 b) $-C_{1-5}$alkoxy, unsubstituted or substituted with -OH,
 c) -OH,
 d) $-O\overset{\overset{O}{\|}}{C}R^7$;
 e) $-COOR^2$

f) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH, or
 iv) halogen,
g) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH,
 iv) C_{1-3}alkyl-NR^2R^2
h) $-NR^2R^2$,
i) $-C_{3-6}$cycloalkyl,

2) aryl, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl,
b) $-C_{1-5}$alkoxy,
c) -OH,
d) halogen,

3) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH,

4) $-C_{1-5}$alkoxy,
5) -OH,
6) $-C_{3-6}$cycloalkyl, or
7) hydrogen;

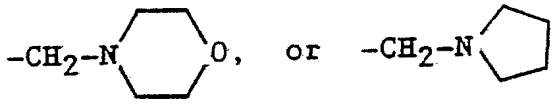
R^4 is 1) R^1 or
2) $-\overset{\overset{O}{\|}}{C}R^1$;

R^5 is 1) R^1,
2) $-C_{1-5}$alkoxy,
3) $-NHR^1$, or
4) heterocycle, unsubstituted or substituted with one or more of:
i) $-C_{1-5}$alkyl,
ii) $-C_{1-5}$alkoxy,
iii) -OH;

R^6 is 1) hydrogen,
2) $-\overset{\overset{O}{\|}}{C}R^1$, or
3) $-\overset{\overset{O}{\|}}{C}NHR^1$; and

R^7 is 1) aryl, unsubstituted or substituted with one or more of -Cl, -Br, -OH, $-OCH_3$, or -CN, or
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH or $-NR^2R^2$,

with the proviso that when X is -H, Y is -S, R is unsubstituted phenyl and R^6 is -H,
Z is not $-CH_2-\overset{\overset{O}{\|}}{S}-Ph$, $-\overset{\overset{O}{\|}}{C}H$,



or a pharmaceutically acceptable salt or ester thereof.

A preferred embodiment of this invention encompasses compounds of Formula A further limited to:

X is -H, -Cl or -F;
Y is $-S(O)_n-$ or $-CH_2-$;
R is -Ph, or -tolyl;
R^6 is -H; and
Z is $-\overset{\overset{W}{\|}}{C}-NR^2R^3$, $-\overset{\overset{O}{\|}}{C}-OR^1$, $-\overset{\overset{O}{\|}}{C}-R^1$,
$-CR^2R^2-\underset{\underset{(O)_n}{|}}{S}-R^1$ or
$-C_{1-3}$alkyl substituted with heterocycle.

A second, more preferred embodiment is further limited to compounds wherein

X is -H or -Cl;
Y is $-S(O)_n-$;
R is -Ph, or -tolyl;
R^6 is -H; and

Z is $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H and W is -O or -S, or

$-CR^2R^2-\overset{\overset{O}{\|}}{S}$-aryl, wherein the aryl group is unsubstituted or substituted with one or more of C_{1-5}alkyl.

A third, most preferred embodiment is further limited to compounds wherein

X is -Cl;

Y is $-S(O)_n-$;

R is -Ph;

R^6 is -H;

Z is $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H, and W is -O or -S; and

R^3 is 1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of

a) $-C_{1-5}$alkoxy, unsubstituted or substituted with -OH,

b) -OH,

c) $-OC\overset{\overset{O}{\|}}{R^7}$,

d) aryl, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH,

ii) $-C_{1-5}$alkoxy,

iii) -OH,

e) heterocycle, unsubstituted or substituted with one or more of:

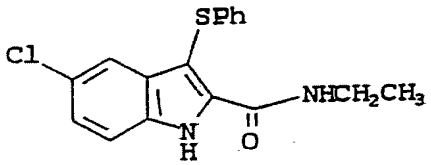
i) $-C_{1-5}$alkyl,
ii) $-C_{1-5}$alkoxy, or
iii) -OH,

2) heterocycle, unsubstituted or substituted with one or more of:
i) $-C_{1-5}$alkyl,
ii) $-C_{1-5}$alkoxy, or
iii) -OH, or

3) hydrogen.

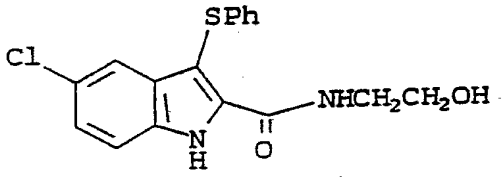
The most preferred compounds of this invention are compounds 1 through 18, shown below.

Compound 1:



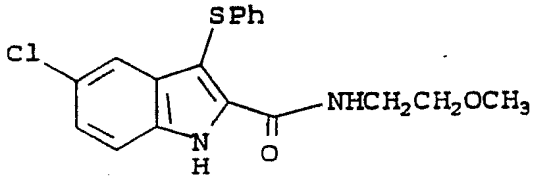
N-ethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 2:



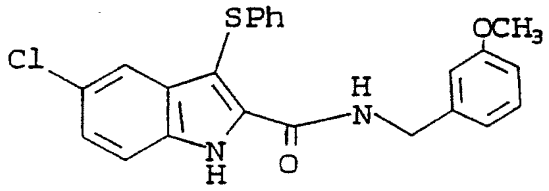
N-2-hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 3:



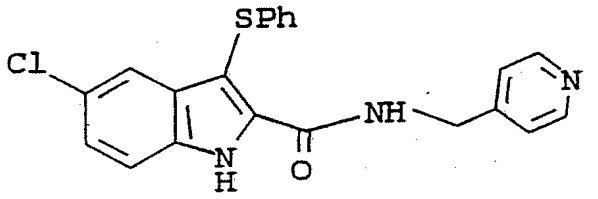
N-2-methoxyethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 4:



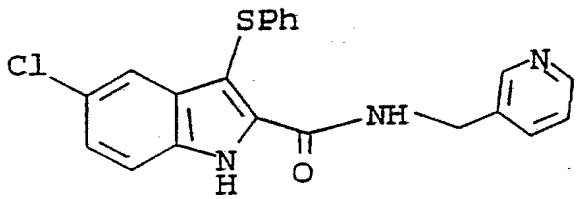
N-3-methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 5:



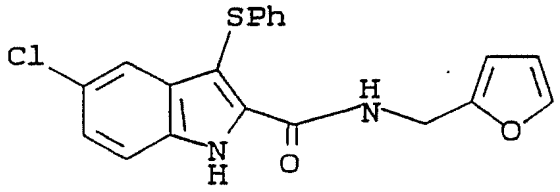
N-4-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 6:



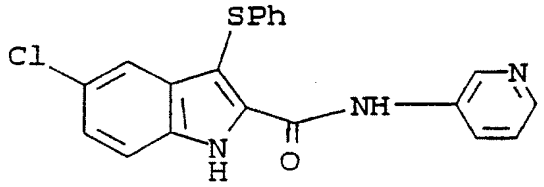
N-3-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 7:



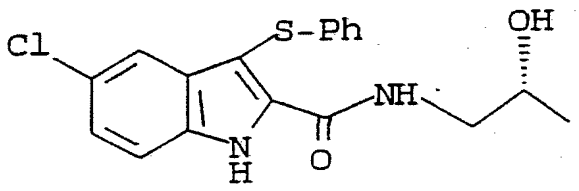
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 8:



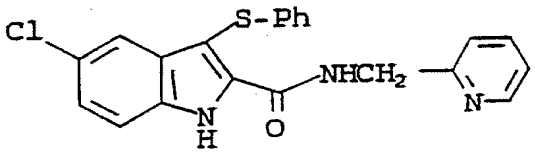
N-3-pyridyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 9:



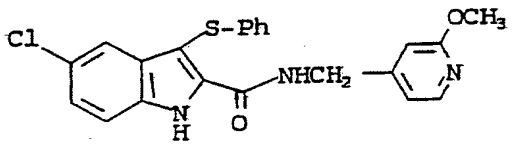
N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenyl-thioindole-2-carboxamide

Compound 10:



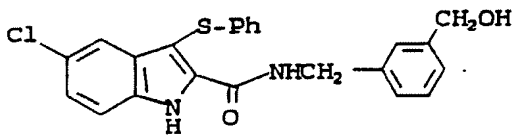
N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 11:



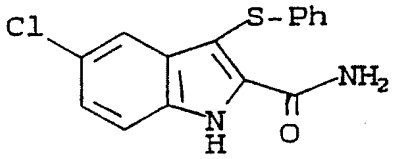
N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenyl-thioindole-2-carboxamide

Compound 12:



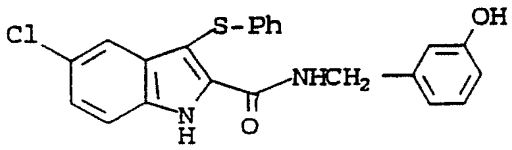
N-(3-hydroxymethyl)benzyl-5-chloro-3-phenyl-thioindole-2-carboxamide

Compound 13:



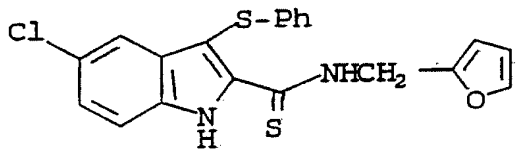
5-chloro-3-phenylthioindole-2-carboxamide

Compound 14:



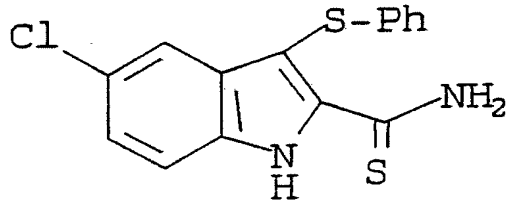
N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide

Compound 15:



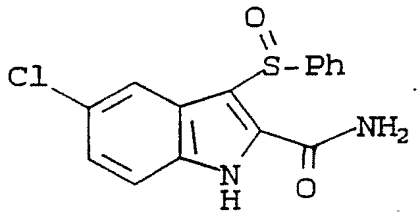
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide

Compound 16:



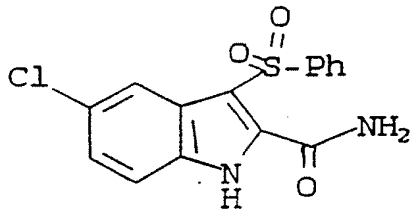
5-chloro-3-phenylthioindole-2-thiocarboxamide

Compound 17:



5-chloro-3-phenylsulfinylindole-2-carboxamide

Compound 18:



5-chloro-3-phenylsulfonylindole-2-carboxamide.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., aryl, heterocycle, R^1, R^2, R^3, etc.) occurs more than one time in any constituent or in formula A of this invention, its definition on each occurrence is independent of its definition at every other occurrence. Also,

combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein, means fluoro, chloro, bromo and iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, biphenyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl,

pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, benzofuranyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl.

Further abbreviations that may appear in this application are as follows:

Me	methyl
Et	ethyl
Ph	phenyl
BuLi	butyllithium
$n\text{-}Bu_3P$	tri-n-butyl phosphine
LAH	lithium aluminum hydride
DMF	dimethylformamide
THF	tetrahydrofuran
Et_3N	tri-ethylamine
MMPP	monoperoxyphthalic acid, magnesium salt
BOP-reagent	benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate
mp or m.p.	melting point

The pharmaceutically-acceptable salts of the novel compounds of this invention that are capable of salt formation (in the form of water- or oil- soluble

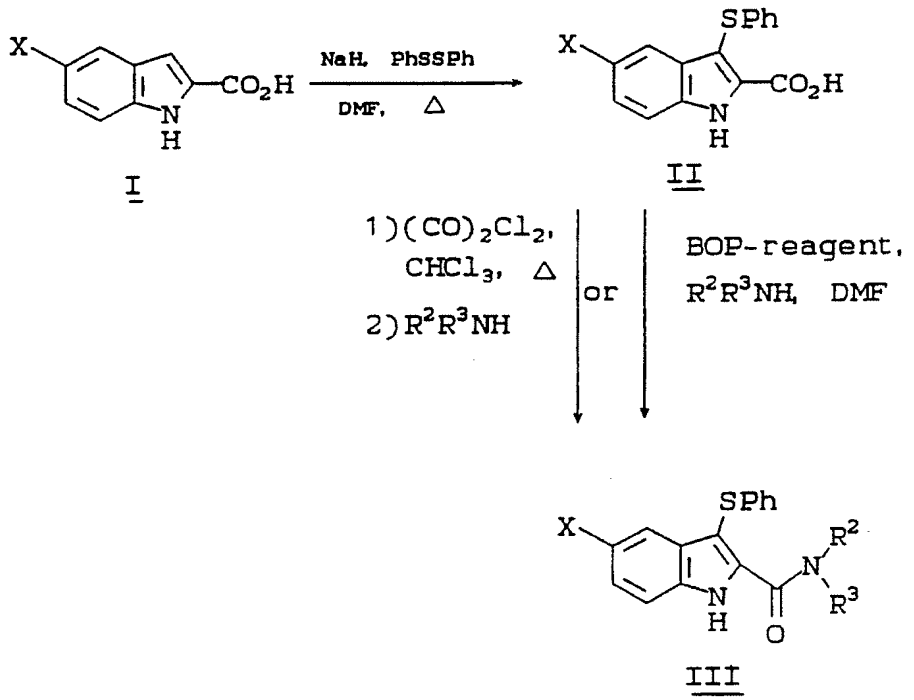
or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts of these compounds, which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bissulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Esters are also encompassed by the present invention, and include those which would readily occur to the skilled artisan, for example, C_{1-4} alkyl esters.

Schemes I-VII for preparing the novel compounds of this invention are presented below. Tables I - VII which follow the schemes illustrate the compounds that can be synthesized by Schemes I-VII, but Schemes I - VII are not limited by the compounds in the tables nor by any particular substituents employed in

the schemes for illustrative purposes. The examples specifically illustrate the application of the following schemes to specific compounds.

Scheme I, below, is a general route for synthesizing, e.g., the compounds shown in Table I, infra. The substituent groups (e.g., X, R, R^1, etc.) employed in Scheme I correspond to the substituent groups as defined in Table I, but Scheme I is not limited by the defined substituents or compounds of Table I.

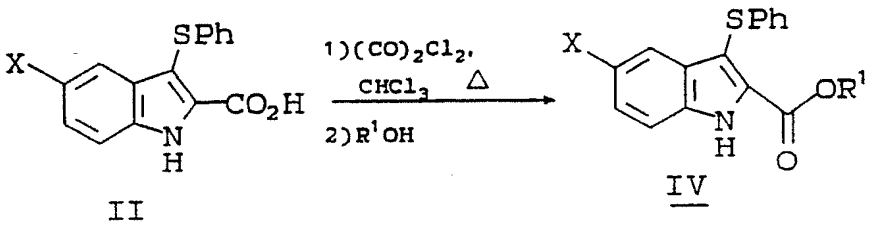
SCHEME I



As shown in Scheme I, commercially available indole-2-carboxylic acid (or 5-chloro, 5-fluoro or 5-methoxyindole-2-carboxylic acid) I is treated with an excess of sodium hydride in dimethylformamide in the presence of an aryl disulfide such as phenyldisulfide at 0°C to 60°C, according to the general procedure described by Atkinson, et al. in Synthesis, p. 480-481 (1988). The resulting product II is reacted with oxalyl chloride in refluxing chloroform for about 30 minutes to 1 hour to produce the corresponding acid chloride which is then reacted with a primary or secondary amine in chloroform at 0°C to 20°C to give the amide III. Alternatively, amide III can be produced directly from II by treatment with BOP reagent (benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate) in the presence of the desired primary or secondary amine and triethylamine, in a solvent such as dimethylformamide. Saponification of ethyl 5-chloro-3-benzylindole-2-carboxylate (prepared as described below) by methods familiar to those skilled in the art, yields 5-chloro-3-benzylindole-2-carboxylic acid, which can be converted to the desired amides in the manner described for the synthesis of amides III.

The compounds shown in Table II infra, are generally synthesized as in Scheme I, except R^1OH is used in place of R^2R^3NH, as depicted in Scheme II below. The substituent groups employed in Scheme II correspond to the substituent groups as defined in Table II, but Scheme II is not limited by the defined substituents or compounds of Table II.

SCHEME II

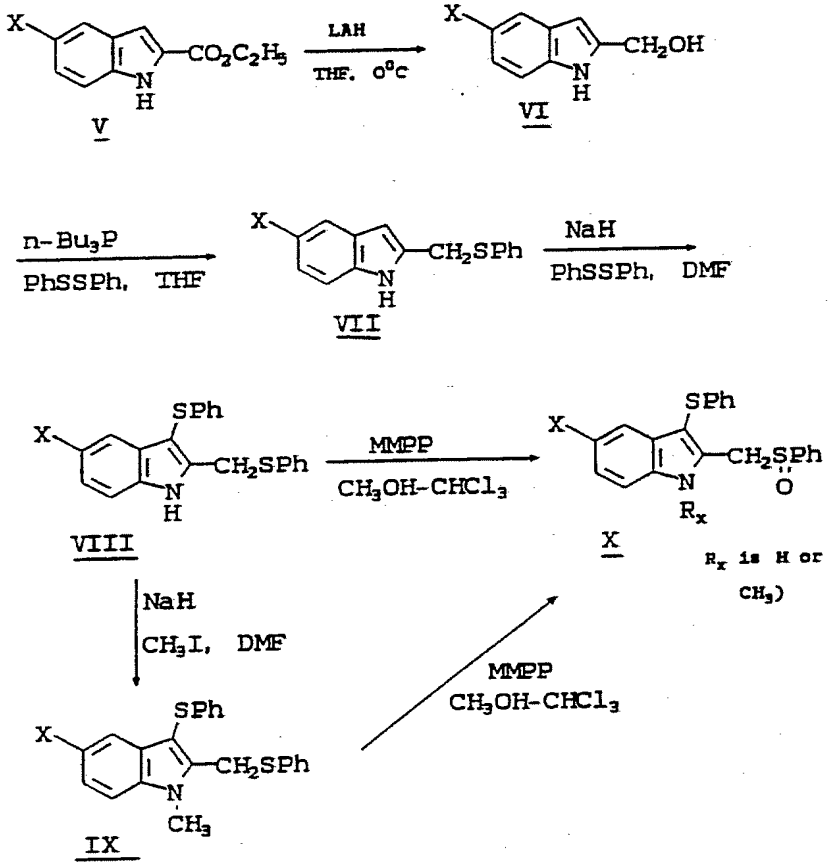


II IV

As shown in Scheme II, 3-phenylthioindole-2-carboxylic acid II can be converted to the corresponding acid chloride with oxalyl chloride in refluxing chloroform, and reacted with an alcohol to give the ester IV. The compound ethyl 5-chloro-3-benzylindole-2-carboxylate was prepared according to the procedure described by Inaba, et al., in Chem. Pharm. Bull., 24, p. 1076-1082 (1976).

Scheme III, below, is a general route for synthesizing, e.g., the compounds shown in Table III, infra. The substituent groups employed in Scheme III correspond to the substituent groups as defined in Table III, but Scheme III is not limited by the defined substituents or compounds of Table III.

SCHEME III

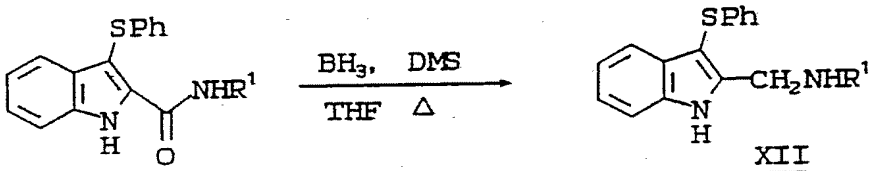


As shown in Scheme III, commercially available ethyl indole-2-carboxylate (compound V wherein X is -H) or ethyl 5-chloroindole-2-carboxylate (compound V wherein X is -Cl), was reduced to the primary alcohol VI with an excess of lithium aluminum hydride in tetrahydrofuran at 0°C. Compound VI was converted to the sulfide VII by treatment with an excess of tri-n-butylphosphine and an aryldisulfide

such as phenyldisulfide in tetrahydrofuran at 0°C to 20°C for 6-24 hours. Reaction of sulfide VII with sodium hydride, an aryldisulfide such as phenyldisulfide, in dimethylformamide at 0°C to 20°C for 1 to 18 hours produces bis-sulfide VIII. Aryl disulfides which were not commercially available were obtained by oxidation of the commercially available aryl mercaptan with dimethyl sulfoxide and iodine, according to the procedure described by Orville G. Lowe in J. Org. Chem., 40, p. 2096-2098 (1975). Compound VIII can be N-alkylated, if desired, by methods familiar to those trained in the art, e.g., by treatment with sodium hydride in dimethylformamide at 0°C in the presence of an alkylating agent such as iodomethane, to give compound IX. Thereafter, compound VIII (or IX) is treated with one equivalent of peracid such as monoperoxyphthalic acid, magnesium salt (MMPP), or meta-chloroperoxy-benzoic acid in methanol or chloroform-methanol at 0°C for 30 minutes to 3 hours, to give predominately sulfoxide X.

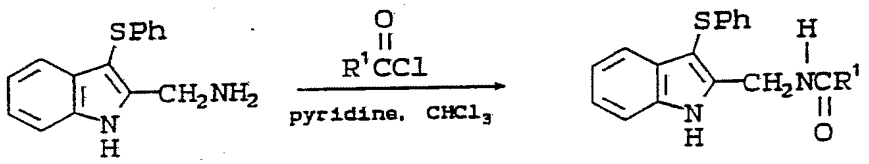
Schemes IV-A and IV-B , below, show a general route for synthesizing, e.g., the compounds shown in Tables IV-A and IV-B, infra. The substituent groups employed in Schemes IV-A and IV-B, respectively, correspond to the substituent groups as defined in Tables IV-A and IV-B, respectively, but Schemes IV-A and IV-B are not limited by the defined substituents or compounds of Tables IV-A and IV-B.

SCHEME IV-A



XI XII

SCHEME IV-B

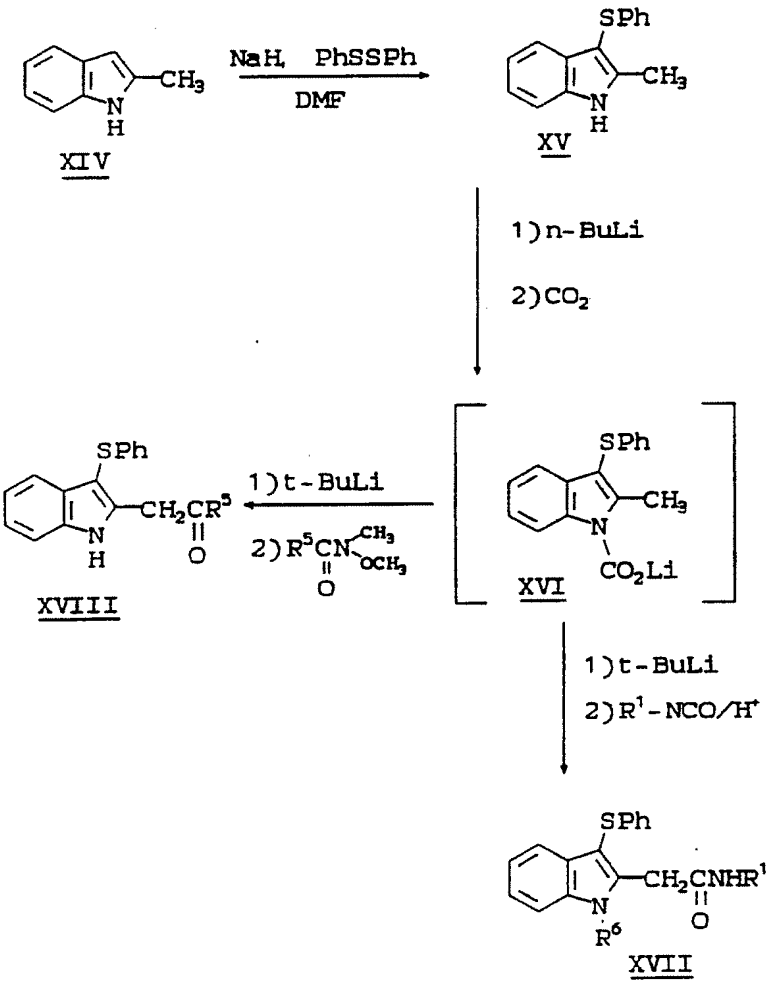


XII-A XIII

As shown in Scheme IV-A, 3-phenylthioindole-2-carboxamides XI can be reduced to primary or secondary amines XII by reaction with an excess of borane-dimethylsulfide complex in refluxing tetrahydrofuran for 6-24 hours. As shown in Scheme IV-B, the primary amine XII-A can be acylated with an acid chloride, such as benzoyl chloride, in chloroform in the presence of pyridine, to give the amide XIII.

Scheme V, below, is a general route for synthesizing, e.g., the compounds shown in Table V-A and Table V-B, infra. The substituent groups employed in Scheme V correspond to the substituent groups as defined in Tables V-A and V-B, but Scheme V is not limited by the defined substituents or compounds of Tables V-A and V-B.

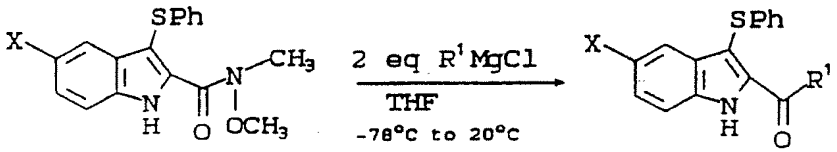
SCHEME V



As shown in Scheme V, commercially available 2-methylindole XIV can be treated with sodium hydride in dimethylformamide in the presence of an aryldisulfide such as phenyldisulfide to give compound XV. Compound XV can be converted to the monoanion with n-butyllithium in tetrahydrofuran at -78°C, and then reacted with carbon dioxide to give carboxylate XVI. The dianion formed by the reaction of XVI with t-butyllithium could be reacted with an isocyanate, such as phenylisocyanate, to give a mixture of monoacylated product and diacylated product XVII (see Table V-B). Alternatively, the dianion formed by the reaction of XVI with t-butyllithium could be reacted with an N-methoxy-N-methyl amide such as N-methoxy-N-methyl-furan-2-carboxamide (prepared in a manner familiar to those skilled in the art, e.g., by the methods described in Scheme 1) to produce ketones XVIII. The methodology described above is essentially that used by A. J. Katritsky and K. Akutagawa to prepare 2-indoleacetic acids, and is published in J. Am. Chem. Soc., 108, 6808 (1986).

Scheme VI, below, is a general route for synthesizing, e.g., the compounds shown in Table VI, infra. The substituent groups employed in Scheme VI correspond to the substituent groups as defined in Table VI, but Scheme VI is not limited by the defined substituents or compounds of Table VI.

SCHEME VI

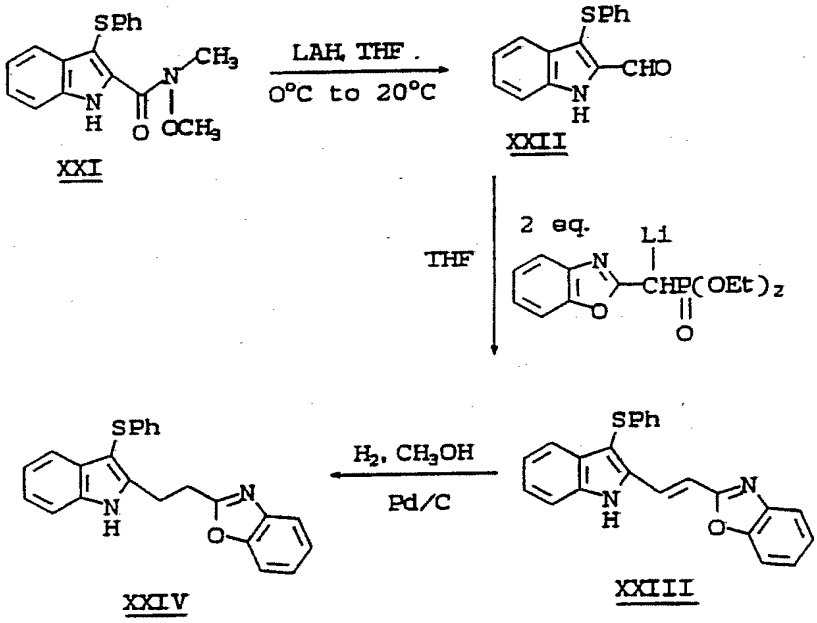


XIX XX

As shown in Scheme VI, N-methoxy-N-methyl-3-phenylthioindole-2-carboxamide XIX (or N-methoxy-N-methyl-5-chloro-3-phenylthioindole-2-carboxamide) (prepared as in Scheme 1) can be reacted with Grignard reagents (wherein R^1 is not hydrogen) such as phenylmagnesium chloride, in tetrahyrodrofuran at -78°C to 20°C for 18-48 hours, or XIX can be reacted with other organometallic reagents well known in the art to one of ordinary skill, to produce ketones XX.

The compounds shown in Table VII infra, can generally be synthesized by those of ordinary skill in the art according to methods described in Schemes I through VI, with the exception of 2-(2-benzoxazol-2-ylethyl)-3-phenylthioindole (compound XXIV), the synthesis of which is described below in Scheme VII.

SCHEME VII

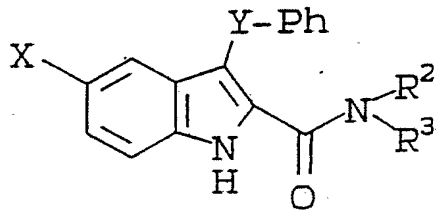


As shown in Scheme VII, N-methoxy-N-methyl-3-phenylthioindole-2-carboxamide XXI can be reduced to aldehyde XXII with lithium aluminum hydride in tetrahydrofuran at 0°C to 20°C for 2-4 hours. Aldehyde XXII could be reacted with the lithium salt of [(benzoxal-2-yl)methyl]diethyl-phosphonate to produce olefin XXIII, which is then hydrogenated in the presence of 10% palladium on charcoal in methanol under one atmosphere of hydrogen to give compound XXIV.

The compound 5-chloro-2-cyano-3-phenylthioindole in Table VII can be prepared by dehydro-sulfurization of 5-chloro-3-phenylthioindole-2-thiocarboxamide with, e.g., $Hg(OAc)_2$.

Using methods well-known to those skilled in the art, compounds of formula A where Y is -SO- or $-SO_2-$ can be synthesized by treatment of compounds where Y is -S- with a suitable oxidizing agent such as, for example, meta-chloroperoxybenzoic acid (MCPBA), sodium periodate or hydrogen peroxide in an appropriate solvent such as MeOH, $CHCl_3$ or acetic acid, or potassium persulfate in a solvent such as $MeOH/H_2O$.

TABLE I



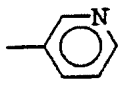
X	Y	R^2	R^3	m.p.
H	S	CH_3	CH_3	194-195°C
H	S	H	CH_2Ph	179-181°C
H	S	H	Ph	194-196°C
H	S	H	$n-C_4H_9$	161-163°C
H	S	H	CH_2CH_2Ph	147-149°C
Cl	S	CH_3	OCH_3	57-59°C
Cl	S	H		255-256°C
H	S	H	CH_3	197-199°C

TABLE I. Cont'd

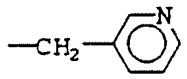
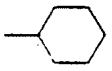
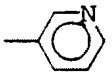
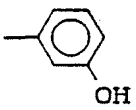
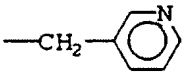
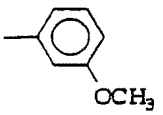
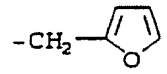
X	Y	R^2	R^3	m p.
Cl	S	H	nC_3H_7	210-212°C
Cl	S	H		240-241°C
Cl	S	H		255-256°C
F	S	H		239-241°C
Cl	S	H		232-233°C
Cl	CH_2	H		243-244°C
Cl	S	H		221°C
Cl	S	H		214°C

TABLE I. Cont'd

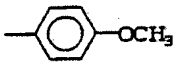
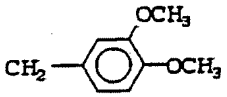
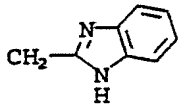
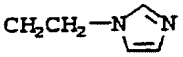
X	Y	R^2	R^3	m p.
Cl	S	H	$-CH_2CH_2CH_2OH$	215°C
Cl	S	H		229°C
Cl	S	H	CH_3	220-221°C
Cl	S	H	$CH_2CH_2CH_2OCH_3$	170-171°C
Cl	S	H		184°C
Cl	S	H		259-260°C (HCl salt)
Cl	S	H		256°C (HCl salt)
Cl	S	H	$CH(CH_3)_2$	193-194°C
Cl	S	CH_3	Ph	191-192°C

TABLE I. Cont'd

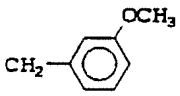
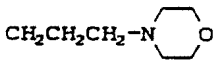
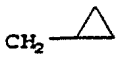
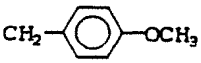
X	Y	R^2	R^3	m.p.
Cl	S	H	$CH_2CH_2CH_2N(CH_3)_2$	229-230°C (HCl salt)
Cl	S	H	C_2H_5	210-211°C
Cl	S	H	Ph	245-246°C
Cl	S	H		172°C
Cl	S	H		162-164°C
Cl	S	H		219-219.5°C
Cl	S	H	CH_2Ph	222°C
Cl	S	H		198°C
Cl	S	H	$CH_2CH_2OCH_2CH_2OH$	161.5-162.5°C

TABLE I. Cont'd

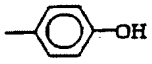
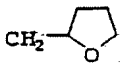
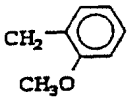
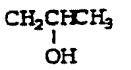
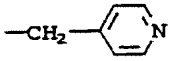
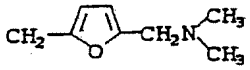
X	Y	R^2	R^3	m.p.
Cl	S	H		>300°C
Cl	S	H	$CH_2CH_2OCH_3$	216-217.5°C
Cl	S	H	$CH_2CH_2OC_2H_5$	165.5-167°C
Cl	S	H		182-183°C
Cl	S	H		201°C
Cl	S	H		205°C
Cl	S	H		228-229°C
Cl	S	H	CH_2CH_2OH	222-223.5°C
Cl	S	H		151-152°C

TABLE I, Cont'd

X	Y	R^2	R^3	mp
Cl	S	H	OCH_3	179-180°C
Cl	S	H	$-CH(CH_2OH)-CH_2CH_3$	153-154°C
Cl	S	H	$-CH_2COC_2H_5$ (O)	215-215.2°C
Cl	S	H	$-CH(CH_3)CH_2OCH_3$	168-169°C
Cl	S	H	$-CH_2$-(OH)	202-203°C
Cl	S	H	$-CH_2$-(N)	209-210°C

TABLE I. Cont'd

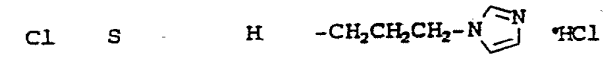
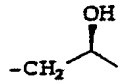
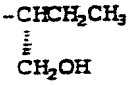
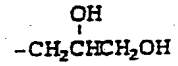
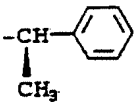
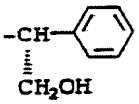
X	Y	R^2	R^3	mp
Cl	S	H		188-189°C
Cl	S	H		205-206°C
Cl	S	H		138-139°C
Cl	S	H		137.5-139°C
Cl	S	H		219-221°C
Cl	S	H		208-210°C
Cl	S	H		223-226°C

TABLE I, Cont'd

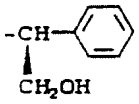
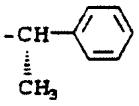
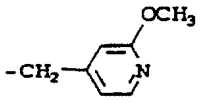
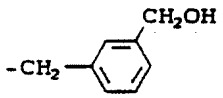
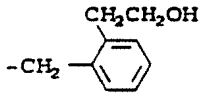
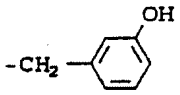
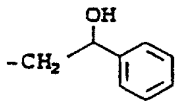
X	Y	R^2	R^3	mp
Cl	S	H		223-226°C
Cl	S	H		208-210°C
Cl	S	H		227-228°C
Cl	S	H		229-230°C
Cl	S	H		217-219°C
Cl	S	H		214-216°C
Cl	S	H		193-195.5°C
Cl	S	H	-H	213-215°C

TABLE I, Cont'd

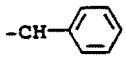
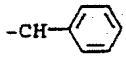
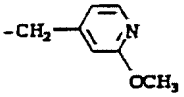
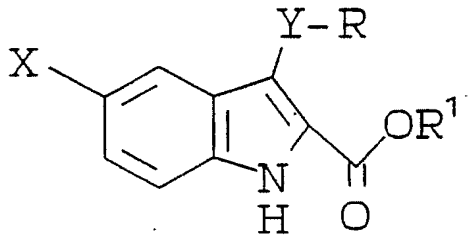
X	Y	R^2	R^3	mp
Cl	SO_2	H	H	255-257°C
Cl	SO_2	H		
Cl	SO_2	H		
Cl	SO_2	H	$-CH_2CH_2OH$	
Cl	SO_2	H		

TABLE II



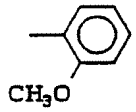
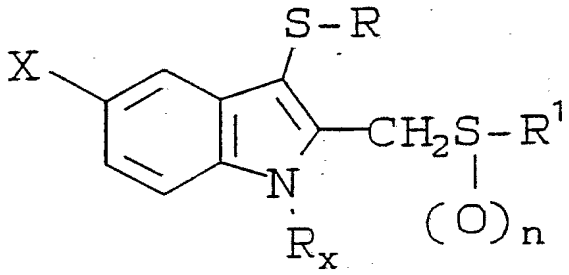
X	Y	R	R^1	mp
H	S	Ph	CH_3	179-180°C
H	S		CH_3	195-197°C
OCH_3	S	Ph	CH_3	211-212°C
Cl	S	Ph	CH_3	193-196°C
Cl	S	Ph	CH_2Ph	154-155°C
Cl	S	Ph	C_2H_5	163-164°C
Cl	CH_2	Ph	C_2H_5	196-197°C
F	S	Ph	C_2H_5	149°C

TABLE III



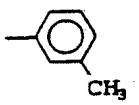
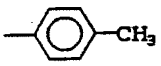
X	R	R^1	n	R_x	mp
H	Ph	Ph	1	H	71-74°C
H	Ph	Ph	0	H	---
H	Ph	Ph	2	H	168-169°C
H		Ph	1	H	166-167°C
H		Ph	1	H	164.5-166.5°C
OCH_3	Ph	Ph	1	H	70-80°C

TABLE III, Cont'd

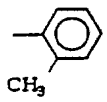
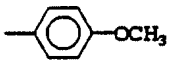
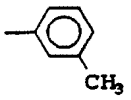
X	R	R^1	n	R_x	mp
H		Ph	1	H	171.5-172.5°C
H	Ph	Ph	0	CH_3	98-99°C
H	Ph	Ph	1	CH_3	177-178°C
H	Ph		1	H	---
H	Ph	CH_3	1	H	164-168°C
H	Ph		0	H	---

TABLE III, Cont'd

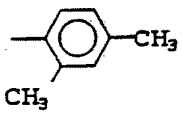
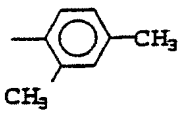
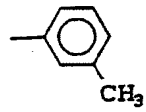
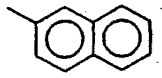
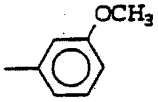
X	R	R^1	n	R_x	mp
H	Ph		0	H	---
H	Ph		1	H	---
H	Ph		1	H	---
H	Ph		1	H	---
H	Ph		1	H	---

TABLE III. Cont'd

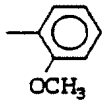
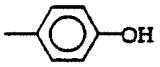
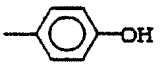
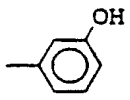
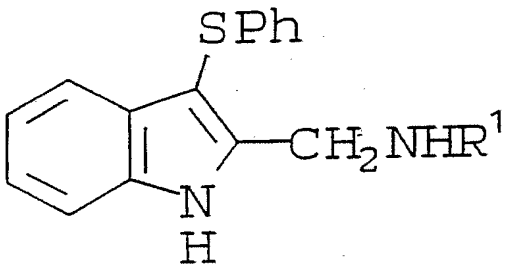
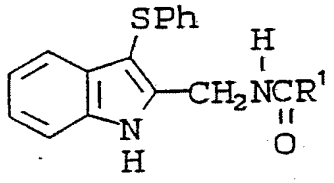
X	R	R^1	n	R_x	mp
H	Ph		1	H	138-140°C
H	Ph		0	H	---
H	Ph		1	H	219-220°C
Cl	Ph	Ph	1	H	158-162°C
H	Ph		1	H	---

TABLE IV-A



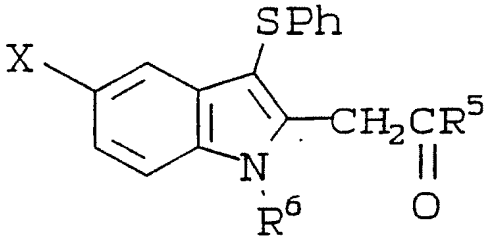
R^1	m p.
$-CH_2Ph$	199-201°C
-Ph	167-170°C
$-n-C_4H_9$	177-179°C
-H	---

TABLE IV-B



R^1	m p.
$-CH_3$	---
-Ph	64-65°C

TABLE V-A



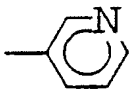
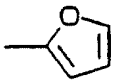
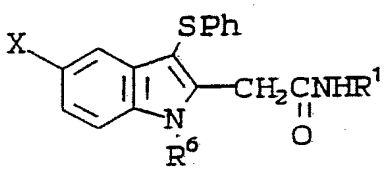
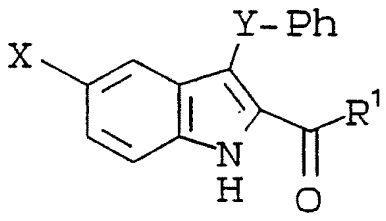
X	R^5	R^6	mp
H	$-CH_2Ph$	H	---
H	-Ph	H	154-155°C
H	$-CH_3$	H	101.5-103.5°C
H		H	87-90°C
H		H	127-129°C
Cl	$-OC_2H_5$	H	99-103°C

TABLE V-B



X	R^1	R^6	mp
H	-Ph	H	66-68°C
H	-Ph	-CNHPh (O)	123-125°C

TABLE VI



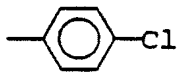
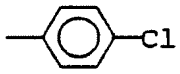
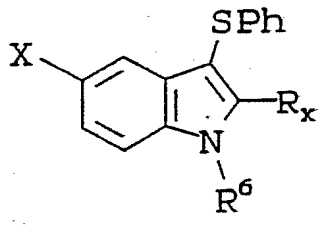
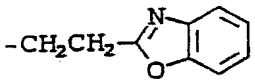
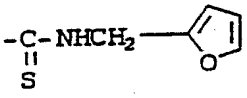
X	Y	R^1	mp
Cl	S	-Ph	154-155°C
Cl	S	$-CH_2Ph$	219-220°C
H	S	-Ph	121.5-123°C
H	S		142-149°C
Cl	S	$-C_2H_5$	196-197°C
Cl	S		214-215°C
Cl	S	$-CH_3$	178°C
Cl	CH_2	$-C_2H_5$	203-205°C
Cl	CH_2	-Ph	161-163°C

TABLE VII



X	R_x	R^6	mp
H	$-CH_3$	H	128-130°C
H	$-CH_3$	$-C(=O)NHPh$	157-159°C
H	$-CH_3$	$-C(=O)Ph$	124-125°C
H	$-CH_2CH_2Ph$	H	117-120.5°C
H		H	192-193°C
Cl	-CN	H	172-174°C
Cl		H	143-144°C
Cl	$-C(=S)-NH_2$	H	217 (decomp.)

The compounds of the present invention are useful in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending

agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV reverse transcriptase inhibitor compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in

combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines include in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

REVERSE TRANSCRIPTASE ASSAY

The assay measures the incorporation of tritiated deoxyguanosine monophosphate by recombinant HIV reverse transcriptase (HIV RT_R) (or other RT) into acid-precipitable cDNA at the Km values of dGTP and poly r(C)•oligo $d(G)_{12-18}$. The inhibitors of the present invention inhibit this incorporation.

Thirty uL of a reaction mixture containing equal volumes of: 500 mM Tris•HCl (pH 8.2), 300 mM $MgCl_2$, 1200 mM KCl, 10 mM DTT, 400 µg/mL poly r(c)•oligo d(G) [prepared by dissolving 1.5 mg (25 U) poly r(C)•oligo d(G) in 1.5 ml sterile distilled H_2O and diluting to 400 µg/ml], 0.1 µCi/µl [^3H] dGTP, 160 µM dGTP, was added to 10 µl sterile distilled H_2O, 2.5 µl of potential inhibitor and 10 µL of 5 nM purified HIV RT_R in tubes. The mixture was incubated at 37°C for 45 minutes.

After incubation is complete, the tubes were cooled in ice for 5 minutes. Ice-cold 13% TCA containing 10 mM $NaPP_i$ (200 µl) are added and the mixture incubated on ice for 30 minutes. The

precipitated cDNA is removed by filtration using presoaked glass filters [TCA, $NaPP_i$]. The precipitate is then washed with 1N HCl, 10 mM $NaPP_i$.

The filter discs are then counted in a scintillation counter.

Under these conditions [dGTP] and poly r(C)•oligo $d(G)_{12-18}$ each are approximately equal to the appropriate Km value. Approximately 5-6,000 cpm of [^{3}H] dGMP are incorporated into acid-precipitable material. The RT reaction is concentration- and time-dependent. DMSO (up to 5%) does not affect enzyme activity. Calculated IC_{50} values for the tested compounds of this invention vary from about 6 nM to more than 300 μM. The IC_{50} values of the most preferred compounds range from about 6 nM to about 30 nM.

INHIBITION OF VIRUS SPREAD

A. Preparation of HIV-infected MT-4 Cell Suspension.

MT cells were infected at Day 0 at a concentration of 250,000 per ml with a 1:2000 dilution of HIV-1 strain IIIb stock (final 125 pg p24/ml; sufficient to yield $\leq$ 1% infected cells on day 1 and 25-100% on day 4). Cells were infected and grown in the following medium: RPMI 1640 (Whittaker BioProducts), 10% inactivated fetal bovine serum, 4 mM glutamine (Gibco Labs) and 1:100 Penicillin-Streptomycin (Gibco Labs).

The mixture was incubated overnight at 37°C in 5% CO_2 atmosphere.

B. Treatment with Inhibitors

Serial two-fold dilutions of compound were prepared in cell culture medium. At Day 1, aliquots of 125 µl of compound were added to equal volumes of HIV-infected MT-4 cells (50,000 per well) in a 96-well microtiter cell culture plate. Incubation was continued for 3 days at 37°C in 5% CO_2 atmosphere.

C. Measurement of Virus Spread

Using a multichannel pipettor, the settled cells were resuspended and a 125 µl harvested into a separate microtiter plate. After the settling of the cells, the plates were frozen for subsequent assay of the supernatant for HIV p24 antigen.

The concentration of HIV p24 antigen was measured by an enzyme immunoassay, described as follows. Aliquots of p24 antigen to be measured were added to microwells coated with a monoclonal antibody specific for HIV core antigen. The microwells were washed at this point, and at other appropriate steps that follow. Biotinylated HIV-specific antibody was then added, followed by conjugated streptavidin-horseradish peroxidase. A color reaction occurs from the added hydrogen peroxide and tetramethylbenzidine substrate. Color intensity is proportional to the concentration of HIV p24 antigen.

The cell culture inhibitory concentration (CIC_{95}) for each compound is defined as that concentration which inhibited by greater than 95% the spread of infection, as assessed by a greater than 95% reduction in p24 antigen production relative to untreated controls. The tested compounds of the

present invention were found to have CIC_{95} values ranging from about 3 nM to about 400 nM for preferred species, and up to about 40 μM for others.

EXAMPLE 1

Preparation of N-(3-Pyridylmethyl)-5-chloro-3-phenylthioindole-2-carboxamide

Step A: 5-Chloro-3-phenylthioindole-2-carboxylic acid

To a suspension of sodium hydride (3.0 g, 60% dispersion in oil, 0.076 mol) in dimethylformamide (125 mL) was added 5-chloroindole-2-carboxylic acid (5.0 g, 0.0255 mol) and phenyldisulfide (6.1 g, 0.028 mol). The reaction was heated under nitrogen at 50°C overnight. The reaction was cooled, and additional sodium hydride (1.8 g) and phenyldisulfide (3.6 g) were added and heating continued for 1 h. The reaction was cooled and the dimethylformamide distilled in vacuo. The residue was partitioned between ethyl acetate and water. The aqueous layer was separated and the pH adjusted to pH1 with 10% aqueous hydrochloric acid. The aqueous phase was extracted with ethyl acetate, and the ethyl acetate extract was washed with water and saturated brine, and dried over magnesium sulfate. The crude product was recrystallized from ethyl acetate in hexane to afford the title compound as an off-white solid.

Step B: N-(3-Pyridylmethyl)-5-chloro-3-phenylthioindole-2-carboxamide

Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (0.73 g, 1.6 mmol) was added to a solution of 5-chloro-3-phenylthioindole-2-carboxylic acid (0.50 g, 1.6 mmol), 3-aminomethylpyridine (0.35 g, 3.2 mmol) and triethylamine (0.50 mL, 3.2 mmol) in degassed dimethylformamide (25 mL). The reaction was stirred at room temperature overnight. The precipitated product was filtered and the filter cake washed well with water. The solid was triturated with 30% ethyl acetate in hexane, filtered and dried at 60°C in vacuo for 72 h. The title compound was obtained as an off-white solid, mp 240-241°C. Anal. Calc. for $C_{21}H_{16}ClN_3OS \cdot 0.25 H_2O$: C, 63.31; H, 4.17; N, 10.54. Found: C, 63.34; H, 4.06; N, 10.71. NMR (DMSO-d_6): δ 12.54 (1H, s), 8.91 (1H, t, J=6 Hz), 8.51 (1H, s), 8.42 (1H, d, J=5 Hz), 7.58 (2H, m), 7.45 (1H, m), 7.25 (4H, m), 7.15 (1H, t, J=7 Hz), 7.04 (2H, d, J=8 Hz), 4.58 (2H, d, J=6 Hz).

EXAMPLE 2

Preparation of Methyl 5-chloro-3-phenylthioindole-2-carboxylate

Oxalyl chloride (0.70 mL, 9.6 mmol) was added to a solution of 5-chloro-3-phenylthioindole-2-carboxylic acid (0.97 g, 3.2 mmol) in chloroform (50 mL) under nitrogen. The reaction was refluxed

for 3 h, cooled and reduced to dryness in vacuo. The resulting solid was dissolved in chloroform and added to methanol at 0°C. The methanol was removed in vacuo and the crude product chromatographed on silica gel with 20% ethyl acetate in hexane. The title compound was obtained as a solid, mp 193-196°C. Anal. Calc. for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81; N, 4.42. Found: C, 60.09; H, 3.50; N, 4.67.

EXAMPLE 3

Preparation of Ethyl 5-chloro-3-benzylindole-2-carboxylate

The title compound was prepared according to the procedure described by Inaba, S., et al., Chem. Pharm. Bull., 24, 1076-1082 (1976). Recrystallization from benzene gave the title compound as pale yellow needles, mp196-197°C. Anal. Calc. for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.13; N, 4.46. Found: C, 68.64; H, 5.10; N, 4.56.

EXAMPLE 4

Preparation of 2-Phenylsulfinylmethyl-3-phenylthioindole

Step A: 2-Hydroxymethylindole

A suspension of lithium aluminum hydride (2.0 g, 0.20 mol) in tetrahydrofuran (100 mL) was cooled with stirring to 0°C under nitrogen. A solution of ethyl indole-2-carboxylate (10.0 g, 0.052 mol) in tetrahydrofuran was added dropwise, maintaining

the reaction temperature between 0-5°C. After 1 h, the reaction was quenched with saturated sodium potassium tartrate solution. The reaction was filtered and the filter cake washed well with tetrahydrofuran. The tetrahydrofuran was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The ethyl acetate solution was washed with water, saturated brine, dried over magnesium sulfate, filtered and freed of solvent. The title compound was obtained as a yellowish solid. NMR ($CDCl_3$): δ 8.18 (1H, bs), 7.57 (1H, d, J=8 Hz), 7.35 (1H, d, J=8 Hz), 7.26 (1H, s), 7.18 (1H, dt, J=1, 8 Hz), 7.10 (1H, dt, J=1, 8 Hz), 6.41 (1H, bs), 4.84 (2H, s).

Step B: 2-Phenylthiomethylindole

2-Hydroxymethylindole (6.94 g, 0.047 mol) and phenyldisulfide (10.8 g, 0.049 mol) were dissolved in tetrahydrofuran (200 mL) and cooled to 0°C under nitrogen. Tri-n-butylphosphine (11.7 mL, 0.047 mol) was added and the reaction stirred for 1 h. Additional phenyldisulfide (1.5 g, 0.007) and tri-n-butylphosphine (5.1 mL, 0.20 mol) was added, and the reaction stirred at room temperature until complete. The tetrahydrofuran was removed in vacuo and the residue chromatographed on silica gel eluting with 5% ethyl acetate in hexane. The title compound was obtained as clear colorless plates, mp 100-101.5°C. Anal. Calc. for $C_{15}H_{13}NS$: C, 75.27, H, 5.47, N, 5.85. Found: C, 74.52, H, 5.39, N, 5.95.

Step C: 3-Phenylthio-2-phenylthiomethylindole

A suspension of sodium hydride (0.37 g 60% dispersion in oil, 9.4 mmol) in dimethylformamide (50 mL) was cooled to 0°C. 2-Phenylthiomethylindole (1.5 g, 6.3 mmol) was added portionwise, and the reaction stirred at 0°C for 15 min. Phenyldisulfide (1.5 g, 6.9 mmol) was added and the reaction stirred at 20°C for 6 h. The reaction was quenched with water and extracted with ethyl acetate. The organic extract was washed with water, saturated brine and dried over magnesium sulfate. Filtration and evaporation of solvent left an oil which was purified by medium pressure chromatography on silica gel using 5% ethyl acetate in hexane. The title compound was obtained as an oil. Anal. Calc. for $C_{21}H_{17}NS_2 \cdot H_2O \cdot 0.15\ C_4H_8O_2$: C, 68.50; H, 5.33; N 3.60. Found: C, 68.40; H, 4.65; N, 3.86.

Step D: 2-Phenylsulfinylmethyl-3-phenylthioindole

A solution of 3-phenylthio-2-phenylthiomethylindole (0.750 g, 2.94 mmol) in methanol (100 mL) was cooled to 0°C with stirring. Monoperoxyphthalic acid magnesium salt (0.908 g, 80% peracid) in methanol (50 mL) was added slowly dropwise. After addition, the reaction was stirred an additional 30 min., then quenched with 10% aqueous sodium thiosulfate (2 mL). The methanol was removed in vacuo, and the residue partitioned between ethyl acetate and water. The organic phase was washed successively with water and saturated brine, then dried over magnesium sulfate.

Filtration and concentration of the filtrate in vacuo gave an oil which was purified by chromatography on silica gel using 20-30% ethyl acetate in hexane. The title compound was obtained as a foam, mp 71-74°C. Exact mass calculated for $C_{21}H_{17}NOS_2$: 364.082982. Found: 364.084549. NMR (DMSO-d_6) δ 11.82 (1H, s), 7.50 (6H, m), 7.23 (1H, d, J=8 Hz), 7.15 (3 H, m) 7.05 (2H, m) 6.90 2H, m), 4.43 (1H, d, J=13 Hz), 4.38 (1H, d, J=13 Hz).

EXAMPLE 5

Preparation of 2-Phenylcarboxamidomethyl-3-phenylthioindole

Step A: 3-Phenythioindole-2-carboxamide

The title compound was prepared from 3-phenylthioindole-2-carboxylic acid (prepared according to the procedure described by Atkinson, J.G. et al., Synthesis, p. 480-481 (1988), (4.01 g, 0.015 mol), ammonia (large excess), and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (7.2 g, 0.016 mol) in dimethylformamide according to the general procedure described in Example 1 for the preparation of N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide. The title compound was obtained as a pale yellow solid.

Step B: 2-Aminomethyl-3-phenylthioindole

A solution of 3-phenylthioindole-2-carboxamide (1.9 g, 7.1 mmol) in tetrahydrofuran was cooled under nitrogen to 0°C and treated with neat borane-dimethylsulfide complex (7.1 mL, 0.070 mol). The reaction was refluxed for 7 h, cooled to 0°C and quenched with 10% aqueous hydrochloric acid. The solution was adjusted to pH 8 with 20% aqueous sodium hydroxide. The reaction was extracted with ethyl acetate and the organic extract washed with saturated brine, and dried over magnesium sulfate. The title compound was obtained as a pale yellow oil.

Step C: 2-Phenylcarboxamidomethyl-3-phenylthioindole

2-Aminomethyl-3-phenylthioindole (0.85 g, 3.3 mmol) was dissolved in chloroform (15 mL) and cooled under nitrogen to 0°C. Pyridine (2.7 mL, 33 mmol) was added, followed by benzoyl chloride (1.1 mL, 10 mmol). The reaction was stirred at 20°C for 1 h and 10% aqueous hydrochloric acid added. The layers were separated and the organic phase washed successively with water, saturated sodium bicarbonate and saturated brine. The chloroform solution was dried over magnesium sulfate, filtered and evaporated to dryness. The resulting oil was chromatographed on silica gel with 5% ethyl acetate in methylene chloride. The title compound was obtained as a solid, mp 64-65°C. Anal. Calc. for $C_{22}H_{18}N_2OS.0.2\ H_2O$: C, 73.00; H, 5.08; N, 7.74. Found: C, 72.93; H, 5.02; N, 7.66.

EXAMPLE 6

Preparation of 2-(N-Phenylacetamido)-3-phenylthioindole and 2-(N-Phenylacetamido)-1-(phenylcarbamoyl)-3-phenylthioindole

2-Methyl-3-phenylthioindole (0.50 g, 2.1 mmol) (prepared according to the procedure described by Atkinson, J. G., et al., Synthesis, p. 480-481 (1988), was dissolved in dry tetrahydrofuran and cooled under nitrogen to -78°C. A solution of n-butyllithium in hexane (0.83 mL, 2.5 M) was added via syringe. Carbon dioxide was bubbled into the reaction mixture over a period of several minutes; unreacted carbon dioxide was removed by freezing the reaction at liquid nitrogen temperature under high vacuum and warming to -78°C. A solution of t-butyllithium in hexane was added (1.35 mL, 1.7 M) and the reaction stirred for 20 min. Phenylisocyanate (0.23 mL, 2.1 mmol) in tetrahydrofuran (1.5 mL) was added and the reaction stirred at 20°C overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with saturated brine and dried over magnesium sulfate. Filtration and evaporation of solvent left an amber oil. The crude products were chromatographed on silica gel eluting successively with 15%, 20%, and 40% ether in hexane. 2-(N-Phenylacetamido)-3-phenylthioindole was isolated as a solid, mp 66-68°C. Anal. Calc. for $C_{22}H_{18}N_2OS$: C, 72.98; H, 5.01; N, 7.73. Found: C, 72.99; H, 4.87; N, 7.52.

Later fractions contained 2-(N-phenylacetamido)-1-(phenylcarbamoyl)-3-phenylthioindole, mp 123-125°C. Anal. Calc. for $C_{29}H_{23}N_3O_2S$: C, 70.28, H, 4.67, N, 8.47. Found: C, 70.37, H, 4.61; N, 8.34.

EXAMPLE 7

Preparation of 2-(2-Oxo-2-furan-3-yl)ethyl-3-phenylthioindole

Step A: N-Methoxy-N-methylfuran-3-carboxamide

The title compound was prepared from furan-3-carboxylic acid (3.4 g, 0.030 mol), N,O-dimethylhydroxylamine hydrochloride hydrochloride (2.9 g, 0.030 mol) triethylamine (8.3 mL, 0.060 mol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (13.3 g, 0.030 mol) according to the general procedure described in Example 1 for N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide. NMR (DMSO-d_6) δ 8.25 (1H, s), 7.75 (1H, s), 3.70 (3H, s), 3.22 (3H, s).

Step B: 2-(2-Oxo-2-furan-3-yl)ethyl-3-phenylthioindole

The title compound was prepared from N-methoxy-N-methylfuran-3-carboxamide (0.32 g, 2.1 mmol), and 2-methyl-3-phenylthioindole (0.50 g, 2.1 mmol) according to the general procedure described in Example 6 for the preparation of 2-(N-phenylacetamido)-3-phenyl-thioindole. The crude product was chromatographed on silica gel with chloroform. The

title compound was obtained as a pale yellow solid, mp 127-129°C. Anal. Calc. for $C_{20}H_{15}NO_2S$: C, 72.05; H, 4.54; N, 4.20. Found: C, 72.08; H, 4.57; N, 4.24.

EXAMPLE 8

Preparation of 2-Benzoyl-5-chloro-3-phenylthioindole

Step A: N-Methoxy-N-methyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared from 5-chloro-3-phenylthioindole-2-carboxylic acid (1.0 g, 3.30 mmol)) N,O-dimethylhydroxylamine hydrochloride (0.64 g, 6.6 mmol), triethylamine (1.0 mL, 7 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (1.64 g, 3.6 mmol) in dimethylformamide according to the general procedure described in Example 1 for the preparation of N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide.

Step B: 2-Benzoyl-5-chloro-3-phenylthioindole

N-Methoxy-N-methyl-5-chloro-3-phenylthioindole-2-carboxamide (0.24 g, 0.69 mmol) was dissolved in dry tetrahydrofuran (5 mL) and cooled to -78°C under nitrogen. A solution of phenylmagnesium chloride in tetrahydrofuran (0.81 mL, 2M) was added via syringe and the reaction warmed to 20°C overnight. Water and ethyl acetate were added to the

reaction and then separated. The organic phase was washed with water, 5% aqueous hydrochloric acid, saturated sodium bicarbonate, saturated brine, and dried over magnesium sulfate. Filtration and evaporation of solvent gave the crude product which was chromatographed on silica gel with 10% ether in hexane. The title compound was obtained as a solid, mp 154-155°C. Anal. calc. for $C_{21}H_{14}ClNOS$: C, 69.32; H, 3.88; N, 3.85. Found: C, 68.61; H, 3.83; N, 3.83.

EXAMPLE 9

Preparation of 2-(2-Benzoxazol-2-ylethyl)-3-phenylthioindole

Step A: N-Methoxy-N-methyl-3-phenylthioindole-2-carboxamide

The title compound was prepared from 3-phenylthioindole-2-carboxylic acid (1.0 g, 3.7 mmol), N,O-dimethylhydroxylamine hydrochloride (0.54 g, 5.5 mmol), triethylamine (1.5 mL, 11 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (1.64 g, 3.7 mmol) according to the procedure described in Example 1 for N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide.

Step B: 3-Phenylthioindole-2-carboxaldehyde

N-Methoxy-N-methyl-3-phenylthioindole-2-carboxamide (1.57 g, 5.26 mmol) was dissolved in tetrahydrofuran (150 mL) and cooled to 0°C under

nitrogen. A solution of lithium aluminum hydride in tetrahydrofuran (5.76 mL, 1M) was added slowly via syringe and the reaction stirred a total of 1.5 h. Ethyl acetate (30 mL) was added, followed by saturated sodium potassium tartrate solution. The layers were separated and the organic phase washed with saturated brine and dried over magnesium sulfate. Filtration and evaporation of solvent gave the title compound as a yellow solid.

Step C: trans-2-(2-Benzoxazol-2-ylethenyl)-3-phenylthioindole

n-Butyllithium in hexane (3.47 mL, 2.5 M) was added to a solution of [(benzoxal-2-yl)-methyl]diethylphosphonate (2.34 g, 8.68 mmol) in tetrahydrofuran (50 mL) at -78oC under nitrogen. The reaction was stirred for 20 min., and warmed to -20°C. A solution of 3-phenylthioindole-2-carboxaldehyde (1.10 g, 4.34 mmol) in tetrahydrofuran (30 mL) was added and the reaction stirred at 20°C overnight. Ethyl acetate and water were added and the layers separated. The organic layer was washed with saturated brine and dried over magnesium sulfate. The crude product was triturated with 1:1 hexane ethyl acetate and collected by filtration. The title compound was obtained as a yellow solid, mp 260°C. Anal. Calc. for $C_{23}H_{16}N_2OS$: C, 72,32; H, 4.58; N, 7.33. Found: C, 72.41; H, 4.50; N, 7.44.

Step D: 2-(2-Benzoxazol-2-ylethyl)-3-phenylthioindole

A solution of trans-2-(2-benzoxazol-2-ylethenyl)-3-phenylthioindole (0.420 g, 1.14 mmol) in 1:1 methanol/tetrahydrofuran (250 mL) was stirred under 1 atmosphere of hydrogen in the presence of 10% palladium on charcoal (100 mg). Additional catalyst was added as needed to drive the reaction to completion. The catalyst was removed by filtration, and the filtrate concentrated in vacuo. The resulting solid was triturated with 10% ethyl acetate in hexane and collected by filtration to afford the title compound, mp 192-193°C. Anal. calc. for $C_{23}H_{18}N_2OS$: C, 72.80; H, 5.04; N, 7.38. Found: C, 72.78; H, 4.95; N, 7.45.

EXAMPLE 10

Preparation of N-2-Furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 2-aminomethylfuran for 3-aminomethylpyridine. The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from acetonitrile gave the title compound, mp 214°C. Anal. Calc. for $C_{20}H_{15}ClN_2O_2S$: C, 62.74; H, 3.95; N, 7.32. Found: C, 62.27; H, 3.88; N, 7.41.

NMR (DMSO-d_6): δ 12.55 (1H, s), 8.72 (1H, t, J=6 Hz), 7.55 (1H, m), 7.54 (1H, d, J=8 Hz), 7.45 (1H, d, J=2 Hz), 7.15 (1H, tt, J=7, 1 Hz), 7.08 (1H, s), 7.06 (1H, d, J= 8 Hz), 6.35 (1H, m), 6.18 (1H, m), 4.56 (2H, d, J=6 Hz).

EXAMPLE 11

Preparation of N-3-Pyridyl-5-chloro-3-phenylthio-indole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 3-aminopyridine for 3-aminomethyl-pyridine. The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Chromatography on silica gel with 40% ethyl acetate in hexane gave the title compound, mp 255-256°C. Anal. Calc. for $C_{20}H_{15}ClN_3OS$: C, 63.24; H, 3.98; N, 10.74. Found: C, 62.59; H, 3.86; N, 11.06. NMR (DMSO-d_6): δ 12.72 (1H, s), 10.55 (1H, s), 8.85 (1H, d, J=3 Hz), 8.35 (1H, dd, J=5, 1 Hz), 8.14 (1H, dm, J_d=8 Hz), 7.60 (1H, d, J=9 Hz), 7.48 (1H, d, J=2 Hz), 7.40 (1H, dd, J=9, 2 Hz), 7.25 (2H, t, J=7 Hz), 7.16 (1H, m), 7.11 (2H, t, J=7 Hz).

EXAMPLE 12

Preparation of N-Ethyl-5-chloro-3-phenylthio-indole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting ethylamine for 3-aminomethylpyridine.

The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from 2% methanol in ethyl acetate gave the title compound, mp 210-211°C. Anal. Calc. for $C_{17}H_{15}ClN_2OS \cdot 0.5\ H_2O$: C, 60.08; H, 4.74; N, 8.24. Found: C, 60.00; H, 4.18; N, 8.52. NMR (DMSO-d_6): δ 12.49 (1H, s), 8.31(1H, t, J=6 Hz), 7.54 (1H, d, J=9 Hz), 7.43 (1H, d, J= 2 Hz), 7.27 (3H, m), 7.15 (1H, tt, J=7, 2 Hz), 7.07 (2H, m), 3.35(4H, m), 1.06 (3H, t, J=7 Hz).

EXAMPLE 13

Preparation of N-3-Methoxybenzyl-5-chloro-3-phenyl-thioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 3-methoxybenzylamine for 3-amino-methylpyridine. The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from acetonitrile gave the title compound, mp 172°C. Anal. Calc. for $C_{23}H_{19}ClN_2O_2S \cdot 0.3\ H_2O$: C, 64.48; H, 4.61; N, 6.54. Found: C, 64.41; H, 4.38; N, 6.75. NMR (DMSO-d_6): δ 12.55 (1H, s), 8.80 (1H, m), 7.55 (1H, d, J=8 Hz), 7.44 (1H, s), 7.25 (3H, m), 7.15 (2H, m), 7.05 (2H, d, J=7 Hz), 6.80 (3H, m), 4.54 (2H, d, J=6 Hz).

EXAMPLE 14

Preparation of N-2-Methoxyethyl-5-chloro-3-phenyl-thioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 2-methoxyethylamine for 3-amino-methylpyridine. The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered to give the title compound, mp 216-217°C. Anal. Calc. for $C_{18}H_{17}ClN_2O_2S$: 0.25 H_2O: C, 59.17; H, 4.83; N, 7.67. Found: C, 59.11; H, 4.75; N, 7.82. NMR (DMSO-d_6): δ 12.54 (1H, s), 8.44 (1H, t, J=6 Hz), 7.54 (1H, d, J=9 Hz), 7.48 (1H, d, J=2 Hz), 7.28 (3H, m), 7.17 (1H, t, J=7 Hz), 7.10 (2H, m), 3.49 (2H, q, J=6 Hz), 3.37 (2H, t, J=6 Hz), 3.16 (3H, s).

EXAMPLE 15

Preparation of N-4-Pyridylmethyl-5-chloro-3-phenyl-thioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 4-aminomethylpyridine for 3-amino-methylpyridine. The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from acetonitrile gave the title compound, mp 228-229°C. Anal. Calc. for $C_{21}H_{16}ClN_3OS$: 0.2 H_2O: C, 63.45; H, 4.16; N, 10.57. Found: C, 63.33; H, 4.02; N, 10.50. NMR (DMSO-d_6): δ 12.56 (1H, s), 8.92 (1H, t,

J= 6 Hz), 8.38 (1H, d, J=4 Hz), 7.55 (1H, d, J=8 Hz), 7.47 (1H, s), 7.31 (1H, dd, J=8, 2 Hz), 7.25 (1H, d, J=7 Hz), 7.17 (2H, m), 7.05 (1H, d, J=7 Hz), 4.58 (2H, d, J=6 Hz).

EXAMPLE 16

Preparation of N-2-Hydroxyethyl-5-chloro-3-phenyl-thioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 2-hydroxyethylamine for 3-amino-methylpyridine. The dimethylformamide was removed in vacuo, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Chromatography on silica gel with 2% methanol in chloroform gave the title compound, mp 222-223°C. Anal. Calc. for $C_{17}H_{15}ClN_2O_2S$: 0.3 H_2O: C, 57.96; H, 4.46; N, 7.95. Found: C, 57.99; H, 4.26; N, 7.90. NMR (DMSO-d_6): δ 12.50 (1H, s), 8.46 (1H, m), 7.55 (1H, d, J=9 Hz), 7.45 (1H, d, J=1 Hz), 7.28 (3H, m), 7.17 (1H, t, J=6 Hz), 7.13 (2H, m), 4.85 (1H, t), 3.49 (1H, m), 3.43 (1H, m).

EXAMPLE 17

Preparation of 5-Chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting an excess of ammonia gas for 3-aminomethylpyridine and triethylamine. The dimethylformamide and excess ammonia were removed in

vacuo and the residue partitioned between ethyl acetate and 10% hydrochloric acid. The organic phase was washed with water, 5% sodium hydroxide and saturated brine, and then dried over magnesium sulfate. Filtration and evaporation gave a crude product which was chromatographed on silica gel with 30% ethyl acetate in hexane. The title compound was obtained as a white solid mp 213-215°C. Anal. Calc. for $C_{15}H_{11}ClN_2OS \cdot 1/3H_2O$: C,58.35; H, 3.81; N, 9.07. Found: C, 58.33; H, 3.64; N, 9.11. NMR (DMSO-d_6): δ 12.52 (1H, bs), 8.06 (1H, s), 7.76 (1H, s), 7.55 (1H, d, J=9 Hz), 7.44 (1H, s), 7.28 (3H, m), 7.15 (1H, t, J=6 Hz), 7.06 (2H, d, J=8 Hz).

EXAMPLE 18

Preparation of 5-Chloro-3-phenylthioindole-2-thiocarboxamide

A solution of 5-chloro-3-phenylthioindole-2-carboxamide (3.8 g, 12.5 mmol) and [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (5.0 g, 12.5 mmol) in dry THF (110 mL) was refluxed under nitrogen for 16 h. The solvent was removed in vacuo and the residue chromatographed on silica gel with 10% ethyl acetate in hexane. The chromatographed product was triturated with hexane and the yellowish solid collected and dried to give the title compound, mp 217°C (decomposed). Anal. Calc. for $C_{15}H_{11}ClN_2S$: C, 56.50; H, 3.48; N, 8.79. Found: C, 56.75; H, 3.64; N, 8.59. NMR (DMSO-d_6): δ 12.22 (1H, s), 10.31 (1H, s), 9.48 (1H, s), 7.50 (1H, d, J=8 Hz), 7.39 (1H, s), 7.25 (3H, m), 7.13 (1H, t, J=7 Hz), 7.01 (2H, d, J=7 Hz).

EXAMPLE 19

Preparation of N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide

The title compound was prepared according to the procedure described for 5-chloro-3-phenyl-thioindole-2-thiocarboxamide except substituting N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide for 5-chloro-3-phenylthioindole-2-carboxamide. The crude product was chromatographed on silica gel with 3% ethyl acetate in hexane. The title compound was obtained as a bright yellow solid, mp 143-144°C. Anal. Calc. for $C_{20}H_{15}ClN_2OS_2 \bullet H_2O$: C, 57.61; H, 3.62; N, 6.72. Found: C, 57.56; H, 3.58; N, 6.52. NMR (DMSO-d_6): δ 12.27 (1H, s), 10.73 (1H, s), 7.55 (2H, m), 7.39 (1H, s), 7.21 (4H, m), 6.98 (2H, d, J=7 Hz), 6.36 (2H, 4.96 (2H, s).

EXAMPLE 20

Preparation of N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 2(R)-hydroxy-1-propylamine for 3-amino-methylpyridine. The dimethylformamide was removed in vacuo and the residue triturated first with 20% ethyl acetate in hexane then by acetonitrile. The title compound was obtained as an off-white solid, mp 202-203°C. Anal. Calc. for $C_{18}H_{17}ClN_2O_2S \bullet 0.3\ H_2O$: C, 59.01; H, 4.67; N, 7.65. Found: C, 58.91; H,

4.59; N, 7.50. NMR (DMSO-d_6): δ 12.52 (1H, s), 8.45 (1H, t, J=5 Hz), 7.55 (1H, d, J=8 Hz), 7.46 (1H, s), 7.25 (3H, m), 7.15 (3H, m), 4.89 (1H, d, J=5 Hz), 3.74 (1H, m), 3.38 (1H, m), 3.23 (1H, m), 1.00 (3H, d, J=6 Hz).

EXAMPLE 21

Preparation of N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 2-pyridylmethylamine for 3-aminomethyl-pyridine. The dimethylformamide was removed in vacuo and the residue triturated first with 30% ethyl acetate in hexane, then with acetonitrile. The title compound was obtained as a white solid, mp 209-210°C. Anal. Calc. for $C_{21}H_{16}ClN_3OS$: C, 64.03; H, 4.10; N, 10.67. Found: C, 63.51; H, 3.97; N, 10.41. NMR (DMSO-d_6): δ 12.58 (1H, s), 9.15 (1H, t, J=5 Hz), 8.46 (1H, d, J=5 Hz), 7.66 (1H, t, J=8 Hz), 7.57 (1H, d, J=8 Hz), 7.50 (1H, s), 7.25 (5H, m), 7.12 (3H, m), 4.68 (2H, d, J=5 Hz).

EXAMPLE 22

Preparation of N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

Step 1: Preparation of 4-cyano-2-methoxypyridine

A solution of 2-chloro-4-cyanopyridine (1.25 g, 9.1 mmol), prepared as described by D. Libermann, N. Rist, F. Grumbach, S. Cals, M. Moyeux and A.

Rouaix, Bull. Soc. Chim. France, 694 (1958), in methanol was treated with sodium methoxide (0.58 g, 10.9 mmol) and refluxed for 30 minutes. The reaction mixture was cooled, filtered and the filtrate concentrated in vacuo to obtain the crude product as an off-white solid. The crude product was chromatographed on silica gel with 20% ethyl acetate in hexane. The title compound was obtained as a white powder.

Step 2: Preparation of 4-aminomethyl-2-methoxypyridine

A solution of 4-cyano-2-methoxypyridine (0.55 g, 4.1 mmol) in ethanol was hydrogenated at 60 psi H_2 in the presence of 10% Pd/C (100 mg). After 3.5 h the catalyst was removed by filtration through Super-Cel and the filtrate evaporated to give the title compound as a foam.

Step 3: Preparation of N-(3-methoxy-4-pyridylmethyl)-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 4-aminomethyl-2-methoxypyridine for 3-aminomethylpyridine. The dimethylformamide was removed in vacuo and the crude product purified by chromatography on silica gel with 20-40% ethyl acetate in hexane. The title compound was obtained as a white solid, mp 227-228°C. Anal. Calc. for $C_{22}H_{18}ClN_3O_2S$: C, 62.33; H, 4.28; N, 9.91. Found: C, 62.63; H, 4.21; N, 9.92. NMR (DMSO-d_6): δ 12.58

(1H, s), 8.93 (1H), 8.37 (2H, d), 7.56 (1H, d), 7.47 (1H, s), 7.27 (3H, m), 7.18 (2H, m), 7.05 (2H, d), 4.59 (2H, d), 3.30 (3H, s).

EXAMPLE 23

Preparation of N-(3-hydroxymethyl)benzyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 3-hydroxymethylbenzylamine for 3-aminomethylpyridine. The dimethylformamide was removed in vacuo and the crude product recrystallized from acetonitrile. The title compound was obtained as a white solid, mp 229-230°C. Anal. Calc. for $C_{22}H_{17}ClN_2O_2S$: C, 64.61; H, 4.19; N, 6.85. Found: C, 64.20; H, 4.09; N, 6.85. NMR (DMSO-d_6): δ 12.69 (1H, s), 10.33 (1H, s), 7.60 (3H, m), 7.49 (1H, s), 7.30 (4H, m), 7.15 (4H, m), 5.22 (1H, t, J=7 Hz), 4.50 (2H, d, J=7 Hz).

EXAMPLE 24

Preparation of N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in example 1, step B, except substituting 3-hydroxybenzylamine for 3-aminomethylpyridine. The dimethylformamide was removed in vacuo and the crude product was chromatographed on silica gel with 10% methanol in chloroform. The title compound was obtained as a white solid, mp 214-216°C. Anal.

Calc. for $C_{22}H_{17}ClN_2O_2S \cdot 0.3\ H_2O$; C, 63.77; H, 4.04; N, 6.76. Found: C, 63.92; H, 3.88; N, 6.49. NMR (DMSO-d_6): δ 12.55 (1H, s), 9.34 (1H, s), 8.75 (1H, t, J=5 Hz), 7.53 (1H, d, J=8 Hz), 7.45 (1H, s), 7.1-7.65 (4H, m), 7.06 (2H, d, J=7 Hz), 7.01 (1H, t, J=8 Hz), 6.70 (1H, s), 6.62 (2H, m), 4.48 (2H, d, J=5 Hz).

EXAMPLE 25

Preparation of 5-Chloro-3-phenylsulfonylindole-2-carboxamide (Compound 18)

5-Chloro-3-phenylthioindole-2-carboxamide (0.177 g, 0.584 mmol) was dissolved in 25 mL chloroform and cooled to 0°C. 50% By weight meta-chloroperoxybenzoic acid (503 mg, 1.46 mmol) was added and the reaction stirred at 20°C for 6 hours. A 10% aqueous solution of sodium thiosulfate was added and the reaction vigorously stirred for 10 minutes. The layers were separated and the organic phase washed with saturated sodium chloride then dried over magnesium sulfate. The crude product was chromatographed over silica gel eluting with 40% ethyl acetate in hexane. The title compound was obtained as a white powder, mp 255-257°C. NMR (300 MHz, DMSO-d6): δ 13.05 (1H,s), 8.48(1H,s), 8.25(1H,s), 8.03(2H,d,J=8 Hz), 7.95(1H,s), 7.60(4H,m), 7.34(1H,d,J=8 Hz). Anal. Calc. for $C_{15}H_{11}ClN_2O_3S$: C, 53.82; H, 3.31; N, 8.37. Found: C, 53.74; H, 3.29; N, 8.34

EXAMPLE 26

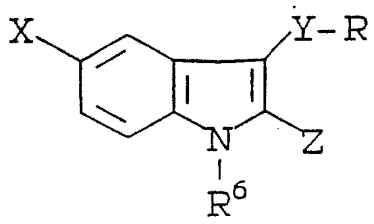
Preparation of 5-Chloro-3-phenylsulfinylindole-2-carboxamide (Compound 17)

A solution of magnesium monoperoxyphthalic acid (85% peracid) (11.8 mg, 0.024 mmol) in methanol (2 mL) was added dropwise to a solution of 5-chloro-3-phenylthioindole-2-carboxamide (14.5 mg, 0.048 mmol) in methanol (2 mL) at 0°C. The reaction was stirred at 20°C for 4 hours. A solution of 10% aqueous sodium thiosulfate was added and the reaction stirred vigorously for 10 minutes. Methanol was removed in vacuo and the residue partitioned between ethyl acetate and water. The ethyl acetate extract was washed with brine and dried over magnesium sulfate. The crude product was purified by column chromatography on silica gel with 30-40% ethyl acetate in hexane. The title compound was obtained as a white solid. NMR (DMSO-d_6, 300 MHz) δ 12.53(1H, s), 8.35(1H,br s), 8.08(1H,br s), 7.83(1H,d,J=2 Hz), 7.71(2H,d,J=8 Hz), 7.52(4H,m), 7.30(1H,dd,J=9,2 Hz).

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, and modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of formula A,



A

wherein

X is -H, -Cl, -F, -Br, $-NO_2$, -CN, or $-OR^2$;

Y is $-S(O)_n-$, $-CR^2R^2-$ or -O-, wherein n is zero, 1 or 2;

R is 1) hydrogen,

2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:

a) $-C_{1-5}$alkyl,

b) $-C_{1-5}$alkoxy,

c) -OH, or

d) aryl, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl,

ii) $-C_{1-5}$alkoxy,

iii) -OH, or

iv) halogen,

3) aryl, unsubstituted or substituted with one or more of:

a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:

i) -OH or

ii) $-C_{1-5}$alkoxy,

b) $-C_{1-5}$alkoxy,
c) -OH, or
d) halogen, or

4) heterocycle, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) $-C_{1-5}$alkoxy,
b) $-C_{1-5}$alkoxy, or
c) -OH;

Z is 1) $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein W is O, S, -N-CN or $-N-OR^1$,

2) $-\overset{\overset{O}{\|}}{C}-OR^1$,

3) $-\overset{\overset{O}{\|}}{C}-R^1$,

4) $-CR^2R^2-\underset{\underset{(O)_n}{|}}{S}-R^1$,

wherein n is defined above,

5) $-CR^2R^2NHR^4$,

6) $-CR^2R^2-\overset{\overset{O}{\|}}{C}-R^5$,

7) $-C_{1-3}$alkyl, unsubstituted or substituted with one or more of:
 a) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH or
 iv) halogen, or
 b) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or
8) -CN;

R^1 is
1) hydrogen,
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl,
 b) $-C_{1-5}$alkoxy,
 c) -OH,
 d) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or
 e) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or

3) aryl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 i) -OH or
 ii) $-C_{1-5}$alkoxy,
 b) $-C_{1-5}$alkoxy,
 c) -OH,
 d) halogen,
 e) -CN,
 f) $-NO_2$, or
 g) $-NR^2R^2$; or
4) heterocycle, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 i) -OH or
 ii) $-C_{1-5}$alkoxy,
 b) $-C_{1-5}$alkoxy, or
 c) -OH;

R^2 is hydrogen or C_{1-3}alkyl;

R^3 is
1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
 a) $-C_{1-5}$alkyl,
 b) $-C_{1-5}$alkoxy, unsubstituted or substituted with -OH,
 c) -OH,
 d) $-O\overset{\overset{O}{\|}}{C}R^7$;
 e) $-COOR^2$

f) aryl, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH, or
 iv) halogen,
g) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH,
 iv) C_{1-3}alkyl-NR^2R^2
h) $-NR^2R^2$,
i) $-C_{3-6}$cycloalkyl,

2) aryl, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl,
b) $-C_{1-5}$alkoxy,
c) -OH,
d) halogen,

3) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy,
 iii) -OH,

4) $-C_{1-5}$alkoxy,
5) -OH,
6) $-C_{3-6}$cycloalkyl, or
7) hydrogen;

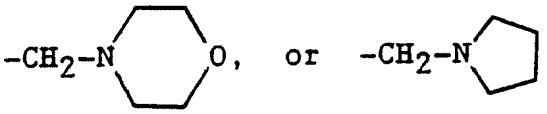
R^4 is 1) R^1 or
2) $-\overset{\overset{O}{\|}}{C}R^1$;

R^5 is 1) R^1,
2) $-C_{1-5}$alkoxy,
3) $-NHR^1$, or
4) heterocycle, unsubstituted or substituted with one or more of:
i) $-C_{1-5}$alkyl,
ii) $-C_{1-5}$alkoxy,
iii) -OH;

R^6 is 1) hydrogen,
2) $-\overset{\overset{O}{\|}}{C}R^1$, or
3) $-\overset{\overset{O}{\|}}{C}NHR^1$; and

R^7 is 1) aryl, unsubstituted or substituted with one or more of -Cl, -Br, -OH, $-OCH_3$, or -CN, or
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH or $-NR^2R^2$,

with the proviso that when X is -H, Y is -S, R is unsubstituted phenyl and R^6 is -H,
Z is not $-CH_2-\overset{\overset{O}{\|}}{S}-Ph$, $-\overset{\overset{O}{\|}}{C}H$,



or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to Claim 1 wherein:
X is -H, -Cl or -F;
Y is $-S(O)_n-$ or $-CH_2-$;
R is -Ph, or -tolyl;
R^6 is -H; and
Z is $-\overset{\overset{W}{\|}}{C}-NR^2R^3$, $-\overset{\overset{O}{\|}}{C}-OR^1$, $-\overset{\overset{O}{\|}}{C}-R^1$,
$-CR^2R^2-\underset{\underset{(O)_n}{|}}{S}-R^1$ or
$-C_{1-3}$alkyl substituted with heterocycle.

3. A compound according to Claim 2 wherein:
X is -H or -Cl;
Y is $-S(O)_n-$;
R is -Ph, or -tolyl;
R^6 is -H; and
Z is $-\overset{\overset{W}{|}}{C}-NR^2R^3$,
wherein R^2 is -H and W is -O or -S, or
$-CR^2R^2-\overset{\overset{O}{\|}}{S}-$aryl, wherein the aryl group is unsubstituted or substituted with one or more of C_{1-5}alkyl.

4. A compound according to Claim 3 wherein:

X is -Cl;

Y is $-S(O)_n-$;

R is -Ph;

R^6 is -H;

Z is $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H, and W is -O or -S; and

R^3 is 1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of

a) $-C_{1-5}$alkoxy, unsubstituted or substituted with -OH,

b) -OH,

c) $-O\overset{\overset{O}{\|}}{C}R^7$,

d) aryl, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH,

ii) $-C_{1-5}$alkoxy,

iii) -OH,

e) heterocycle, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl,

ii) $-C_{1-5}$alkoxy, or

iii) -OH,

2) heterocycle, unsubstituted or substituted with one or more of:
 i) $-C_{1-5}$alkyl,
 ii) $-C_{1-5}$alkoxy, or
 iii) -OH, or
3) hydrogen.

5. The compound,
N-ethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-methoxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-4-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-pyridyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenyl-thioindole-2-carboxamide,
N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenyl-thioindole-2-carboxamide,

N-(3-hydroxymethyl)benzyl-5-chloro-3-phenyl-thioindole-2-carboxamide,
5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide,
5-chloro-3-phenylthioindole-2-thiocarboxamide,
5-chloro-3-phenylsulfinylindole-2-carboxamide, or
5-chloro-3-phenylsulfonylindole-2-carboxamide,

or a pharmaceutically acceptable salt or ester thereof.

6. The compound,
N-ethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-methoxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-4-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide, or
N-3-pyridyl-5-chloro-3-phenylthioindole-2-carboxamide,

or a pharmaceutically acceptable salt or ester thereof.

7. The compound,
N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenyl-thioindole-2-carboxamide,
N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenyl-thioindole-2-carboxamide,
N-(3-hydroxymethyl)benzyl-5-chloro-3-phenyl-thioindole-2-carboxamide,
5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide,or
5-chloro-3-phenylthioindole-2-thiocarboxamide,

or a pharmaceutically acceptable salt or ester thereof.

8. The compound
5-chloro-3-phenylsulfinylindole-2-carboxamide, or
5-chloro-3-phenylsulfonylindole-2-carboxamide,

or a pharmaceutically acceptable salt or ester thereof.

9. A method of inhibiting HIV reverse transcriptase, comprising administering to a mammal an effective amount of a compound as in any of Claims 1-8.

10. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC, comprising administering to a mammal an effective amount of a compound as in any of Claims 1-8.

11. A pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of a compound as in any of Claims 1-8, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS or ARC, comprising an effective amount of a compound as in any of Claims 1-8, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07219

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D209/42; C07D209/30; C07D401/12; C07D405/12
C07D403/12; C07D401/06; C07D405/06; C07D413/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	CHEMICAL ABSTRACTS, vol. 72, no. 3, 19 January 1970, Columbus, Ohio, US; abstract no. 12471D, 'synthesis of 3-benzylindole derivatives' page 313 ; see abstract	1,2
X	CHEMICAL ABSTRACTS, vol. 85, no. 5, 2 August 1976, Columbus, Ohio, US; abstract no. 32754V, 'convenient preparation of 2,3-dialkylindoles' page 374 ; see abstract	1
X	CHEMICAL ABSTRACTS, vol. 87, no. 17, 24 October 1977, Columbus, Ohio, US; abstract no. 135057R, '3-indolyl thio ethers' page 705 ; see abstract	1

-/--

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 NOVEMBER 1992	02. 12. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCRUTON-EVANS I.

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 90, no. 1, 1 January 1979, Columbus, Ohio, US; abstract no. 6272V, 'metal reagents in organic reactions: part II' page 575 ; see abstract	1
X	CHEMICAL ABSTRACTS, vol. 106, no. 7, 16 February 1987, Columbus, Ohio, US; abstract no. 49926C, 'photochemical conversion of 3-azido-2-vinylthiophenes into thienopyrroles and of 2-azidostyrenes into indoles' page 616 ; see abstract	1,2
X	CHEMICAL ABSTRACTS, vol. 109, no. 17, 24 October 1988, Columbus, Ohio, US; abstract no. 149279Z, 'a new synthesis of 3-arylthioindoles' page 710 ; see abstract	1,2
X	CHEMICAL ABSTRACTS, vol. 106, no. 15, 13 April 1987, Columbus, Ohio, US; abstract no. 119608B, 'reactions of organic anions, part 132. A facile synthesis of 3-sulfonyl-substituted indole derivatives' page 618 ; see abstract	1
X	REMERS AND SPANDE 'indoles part three (the chemistry of heterocyclic compounds, v 25)' 1979 , JOHN WILEY AND SONS , USA *pages 306,309,310,314,315,461,462,476,477*	1
X	DE,A,1 935 671 (SUMITOMO CHEMICAL COMPANY LTD.) 5 March 1970 *see claims 1,2,3	1,2
Y	WO,A,9 109 849 (UPJOHN CO.) 11 July 1991 *see claim 1 and 10-12*	1-12
A	CHEMICAL ABSTRACTS, vol. 104, no. 1, 7 July 1986, Columbus, Ohio, US; abstract no. 61594J, 'reversal of feline retroviral suppression by indomethacin' page 26 ; see abstract	1-12

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WO,A,9 105 761 (UNIROYAL CHEM LTD) 2 May 1991 *whole document, especially definition iii for R, with Rz as definition d), and RA as definition 3*	1-12

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9207219 SA 64066

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/11/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		DE-A-	1920207	08-01-70
		DE-A-	1966206	20-01-72
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		EP-A-	0507861	14-10-92
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		CN-A-	1051036	01-05-91
		EP-A-	0497816	12-08-92

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(19) World Intellectual Property Organization
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(25) Filing Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

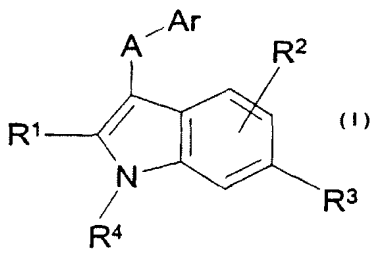
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/029212 A1

(54) Title: INDOLE DERIVATIVES AS COX II INHIBITORS



(I)

(57) Abstract: This present invention relates to indole derivatives of Formula (I); wherein A, Ar and R^1 to R^4 are as defines in the specification. The compounds are useful as a selective COX-II inhibitor and, therefore, may be used for the treatment of COX-II mediated diseases.

INDOLE DERIVATIVES AS COX II INHIBITORS

Indole derivatives

The present invention is directed to indole derivatives that inhibit COX II and therefore useful in the treatment of mammals having disease states mediated by it. The present invention is also directed to medicaments containing these compounds, method for preparing them, and their use.

Non-steroidal, anti-inflammatory drugs (NSAIDs) have a problem of causing serious side-effects such as gastrointestinal tract distress or nephro-toxicity. NSAIDs inhibit the activity of cyclooxygenase (COX), which is an enzyme involved in prostaglandin G/H synthesis, resulting in the inhibition of the biosynthesis of prostaglandins not only in inflammatory loci but also in stomach and kidney. It has been found that COX exists in two forms: COX-I and COX-II, *Cell*, 83, 345, (1995).

COX-I is expressed in normal cells and controls the function of stomach and kidney, while COX-II is induced by mitogens or cytokines in inflammatory sites where inflammation and other immunoreactions occur , *J. Biol. Chem.*, 271, 33157(1996).

To avoid the toxicity of NSAIDs due to the inhibition of coexisting COX-I, selective inhibitors of COX-II have been investigated. The selective COX-II inhibitors have anti-inflammatory action, pain-relieving action, and/or antipyretic action; with less side effects such as bleeding in the gastrointestinal tract. COX-II inhibitors may show anticancer activity, and lower the induction of asthma in asthmatic patients who are sensitive to conventional NSAIDs. These selective inhibitors of COX-II may also be used in treating Alzheimer's disease and osteoporosis of women after menopause.

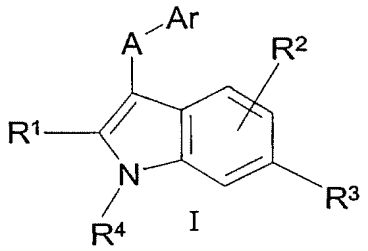
US Patent No.4,654,360 (assigned to Syntex USA) refers to certain new 3-phenylthioindole derivatives useful as lipoxygenase inhibitors.

EP Patent Application EP396,124 (assigned to Searle) refers to certain new indole-2-carboxylate compounds used for treatment of CNS disorders.

PCT Published Patent Applications WO 98/08818 and WO 99/43672 (assigned to Genetics Inst. Inc.) refers to certain benzimidazolyl-, indolyl-, and quinolyl-benzoic acid derivatives used in the treatment of inflammation disorders.

DE German Application DE 4,338,770 (assigned to Lehr) refers to certain indole derivatives useful as phospholipase A2 inhibitors.

In a first aspect, this invention provides compounds selected from the group of compounds represented by Formula I:



I

wherein:

A is a $-CH_2-$, -O-, -S-, or -S(O)-;

Ar is an optionally substituted phenyl or an optionally substituted naphthalenyl;

R^1 is hydrogen, alkyl, alkoxy, hydroxy, hydroxy alkyl, alkylthio, halo, cyano, $-C(O)R^5$, $-C(O)NR^5R^6$, $-NR^5R^6$, $-(CR'R'')_{0-3}OC(O)R^5$, $-(CR'R'')_{0-3}SO_2R^5$ and $-(CR'R'')_{0-3}NSO_2R^5$, wherein R^5, R^6, R', and R'' are each independently in each occurrence hydrogen or alkyl, with the proviso that if A is $-CH_2-$, R^1 is not $-C(O)NR^5R^6$;

R^2 is hydrogen, alkyl, alkoxy, hydroxy, halo, halo alkyl, nitro, cyano, or $-NR^5R^6$, wherein R^5 and R^6 are as defined previously;

R^3 is $-SOR^7$, $-SO_2R^7$, or $-SO_2NR^5R^6$ wherein R^7 is alkyl, hydroxy alkyl, alkoxy alkyl, or alkoxycarbonyl alkyl; and R^5 and R^6 are as defined previously;

R^4 is hydrogen or alkyl;

and prodrugs, individual isomers, mixtures of isomers, and pharmaceutically acceptable salts thereof.

Also, within the compounds as defined above [they will be referred to in the following under (i)], preferred are the following compounds:

(ii) The compound of (i) wherein

A is a $-CH_2-$, -O-, -S-, or -S(O)-;

Ar is an optionally substituted phenyl;

R^1 is hydrogen, alkyl, alkoxy, hydroxy, hydroxy alkyl, alkylthio, halo, cyano, $-C(O)NR^5R^6$, $-NR^5R^6$, $-(CR'R'')_{0-3}OC(O)R^5$, $-(CR'R'')_{0-3}SO_2R^5$, and $-(CR'R'')_{0-3}NSO_2R^5$, wherein R^5, R^6, R' and R'' are each independently in each occurrence hydrogen or alkyl, with the proviso that when A is $-CH_2-$, then R^1 is not $-C(O)NR^5R^6$;

R^2 is hydrogen, alkyl, alkoxy, hydroxy, halo, halo alkyl, nitro, cyano, or $-NR^5R^6$, wherein R^5 and R^6 are as defined previously;

R^3 is $-SOR^7$, $-SO_2R^7$, or $-SO_2NR^5R^6$ wherein R^7 is alkyl, hydroxy alkyl, alkoxy alkyl, or alkoxycarbonyl alkyl; and R^5 and R^6 are as defined previously;

R^4 is hydrogen or alkyl.

(iii) The compound of (i) or (ii) wherein Ar is phenyl optionally substituted at one or two substitutents independently selected from the group consisting of halo and alkoxy, and R^3 is $-SO_2R^7$, wherein R^7 is alkyl.

(iv) The compound of (i), (ii) or (iii) wherein A is -O-.

(v) The compound of any one of (i) to (iv) wherein R^1is alkyl or cyano.

(vi) The compound of any one of (i) to (iii) wherein A is -S-.

(vii) The compound of any one of (i), (ii), (iii) and (vi) wherein R^1 is alkyl, hydroxy alkyl, or cyano.

(viii) The compound of (i), (ii) or (iii) wherein A is $-CH_2-$.

(ix) The compound of any one of (i), (ii), (iii) and (viii) wherein R^1 is alkyl or cyano.

(x) The compound of (i) comprising:

3-(2-Chloro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole;
(6-Methanesulfonyl-3-phenylsulfanyl-1*H*-indol-2-yl)-methanol;
3-(4-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile;
3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile;
3-(4-Fluoro-benzenesulfinyl)-6-methanesulfonyl-2-methyl-1*H*-indole;
3-(4-Fluoro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole.

In a second aspect, this invention provides a medicament containing a therapeutically effective amount of a compound of Formula I or its pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

In a third aspect, this invention provides use of a compound of formula I for the manufacture of medicaments comprising one or more compounds of formula I for the treatment of a disease, in particular an inflammatory or autoimmune disease, in a mammal treatable by administration of a prostaglandin G/H synthase inhibitor.

In a fourth aspect, this invention provides processes for preparing compounds of Formula I.

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, *e.g.*, methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, *e.g.*, methylene, ethylene, propylene, 2-methylpropylene, pentylene.

"Alkoxy", "aryloxy", " aralkyloxy", or "heteroaralkyloxy" means a radical -OR where R is an alkyl, aryl, aralkyl, or heteroaralkyl respectively, as defined herein, *e.g.*, methoxy, phenoxy, benzyloxy, pyridin-2-ylmethyloxy.

"Alkoxycarbonylalkyl" means a radical $-R^aC(O)R^b$ where R^a is an alkylene group as defined above and R^b is an alkoxy group as defined above e.g., methoxycarbonylethyl, ethoxycarbonylbutyl.

"Alkylsulfanyl" means the radical -SR, wherein R is a alkyl radical as defined herein. Examples of alkylsulfanyl radicals include, but are not limited to, methanesulfanyl, butanesulfanyl.

"Alkylsulfinyl" means the radical -SOR, wherein R is a alkyl radical as defined herein. Examples of alkylsulfinyl radicals include, but are not limited to, methanesulfinyl, butanesulfinyl.

"Alkylsulfonyl" means the radical $-SO_2R$, wherein R is a alkyl radical as defined herein. Examples of alkylsulfonyl radicals include, but are not limited to, methanesulfonyl, butanesulfonyl.

"Cycloalkyl" means a saturated monovalent cyclic hydrocarbon radical of three to seven ring carbons. The cycloalkyl may be optionally substituted independently with one, two, or three substituents selected from alkyl, optionally substituted phenyl, or -C(O)R

(where R is hydrogen, alkyl, haloalkyl, amino, acylamino, mono-alkylamino, di-alkylamino, hydroxy, alkoxy, or optionally substituted phenyl). More specifically, the term cycloalkyl includes, for example, cyclopropyl, cyclohexyl, phenylcyclohexyl, 4-carboxycyclohexyl, 2-carboxamidocyclohexyl, 2-dimethylaminocarbonylcyclohexyl.

"Cycloalkylalkyl" means a radical $-R^aR^b$ where R^a is an alkylene group and R^b is a cycloalkyl group as defined herein, *e.g.*, cyclopropylmethyl, cyclohexylpropyl, 3-cyclohexyl-2-methylpropyl.

"Acyl" means the group –C(O)R', where R' is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl, wherein the phenyl group can be optionally substituted.

"Acylamino" means a radical $-R^aR^b$ where R^a is a amino group and R^b is an acyl group as defined herein.

"Monoalkylamino" or "dialkylaminoalkyl" means a radical -NHR or -NRR' respectively, where R and R' are independently alkyl as defined herein, *e.g.*, methylamino, ethylamino, dimethylamino, ethylmethylamino.

"Haloalkoxy" means alkoxy as defined herein substituted with one or more, preferably one to three same or different halogen atoms.

"Heteroalkyl" means an alkyl radical as defined herein with one, two or three substituents independently selected from $-OR^a$, $-NR^bR^c$, and $-S(O)_nR^d$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom of the heteroalkyl radical. R^a is hydrogen, acyl, alkyl, cycloalkyl or cycloalkylalkyl. R^b and R^c are independently of each other hydrogen, acyl, alkyl, cycloalkyl or cycloalkylalkyl. R^d is hydrogen (provided that n is 0), alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, mono-alkylamino or di-alkylamino. Representative examples include, for example, 2-hydroxyethyl, 2,3-dihydroxypropyl, 2-methoxyethyl, benzyloxymethyl, 2-methanesulfonyl-ethyl.

"Phenylalkyl" means a radical $-R^aR^b$ where R^a is an alkylene group as defined herein and R^b is a phenyl group, *e.g.*, benzyl, pheylethyl.

"Aryl" means a monovalent monocyclic or bicyclic aromatic radical of 6 to 10 ring atoms which is substituted independently with one to five substituents, preferably one, two, or three substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, alkylamino, dialkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, cycloalkyl, phenyl or phenylalkyl), -

$(CR'R")_nCOOR$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl) or -$(CR'R")_nCONR^aR^b$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl). More specifically the term aryl includes, but is not limited to, phenyl, biphenyl, 1-naphthyl, and 2-naphthyl, and the derivatives thereof.

"Halogen" or "halo" means the radical fluoro, bromo, chloro, and/or iodo.

"Haloalkyl" means alkyl substituted with one or more same or different halo atoms, *e.g.*, $-CH_2Cl$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and further includes those alkyl groups such as perfluoroalkyl in which all hydrogen atoms are replaced by fluorine atoms.

"Hydroxyalkyl" means an alkyl radical as defined herein, substituted with one or more, preferably one, two or three hydroxy groups, provided that the same carbon atom does not carry more than one hydroxy group. Representative examples include, but are not limited to, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxymethyl-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-hydroxymethyl-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-hydroxymethyl-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl and 1-hydroxymethyl-2-hydroxyethyl. Accordingly, as used herein, the term "hydroxyalkyl" is used to define a subset of heteroalkyl groups.

"Optionally substituted phenyl" means a phenyl ring which is optionally substituted independently with one to four substituents, preferably one or two substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, monoalkylamino, dialkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl, -(CR'R"), -COOR (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), $-(CR'R")_nCONR^aR^b$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), alkylsulfanyl, alkylsulfinyl or alkylsulfonyl, preferably selected from alkyl, cycloalkyl, cycloalkylalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, monoalkylamino, dialkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl, -(CR'R"), -COOR (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), $-(CR'R")_nCONR^aR^b$ (where n is an integer from 0

to 5, R' and R" are independently hydrogen or alkyl, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl).

"Optionally substituted naphthalenyl" means a naphthalenyl ring which is optionally substituted independently with one to four substituents, preferably one or two substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, monoalkylamino, dialkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl, -(CR'R"), -COOR (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), $-(CR'R")_nCONR^aR^b$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), alkylsulfanyl, alkylsulfinyl or alkylsulfonyl.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry i.e., an atom or group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (e.g. acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (e.g., 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

"Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid,

4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, t-butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine,.

"Prodrugs" means any compound which releases an active parent drug, or any compound which changes its oxidation level, according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula I are prepared by modifying functional groups present in the compound of Formula I in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may also be prepared by incomplete oxidation of certain functional groups such as sulfur containing groups, in such a way that the oxidation of said functional groups may be effected *in vivo* to release a compound according to Formula I. Prodrugs include compounds of Formula I wherein a hydroxy, amino, or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives) or carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups, and thiol or sulfoxide groups in compounds of Formula I.

"Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Futs, Protective Groups in Organic Chemistry, (Wiley, 2nd ed. 1991) and Harrison and Harrison *et al.*, Compendium of Synthetic Organic Methods, Vols. 1-8 (John Wiley and Sons. 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethylsilyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC). Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as benzyl and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers, and allyl ethers.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

"A therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity, and the age, weight, etc., of the mammal to be treated.

"Optional" or "optionally" in the above definitions means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclo group optionally mono- or di-substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocyclo group is mono- or di-substituted with the alkyl group and situations where the heterocyclo group is not substituted with the alkyl group.

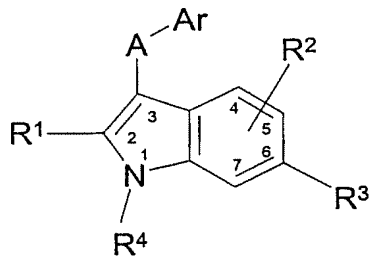
Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog, (Cahn et al. *Angew. Chem. Inter.* Edit., 5, 385; (1966) errata 511; Cahn et al. *Angew. Chem.*, 78, 413; (1966) Cahn and Ingold *J. Chem. Soc.* (London), 612; (1951) Cahn et al. *Experientia*, 12, 81; (1956), Cahn, J. *Chem.Educ.*, 41, 116, (1964)) or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

Throughout the application the following abbreviations are used with the following meanings:

DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl Acetate
HMPA	Hexamethylphosphoric triamide
HPLC	High pressure liquid chromatography
KHMDS	Potassium hexamethyldisilazide
MCPBA	m-Chloroperbenzoic acid
MHz	Megahertz
MS	Mass Spectrum
NMR	Nuclear Magnetic Resonance
OXONE™	Potassium peroxymonosulfate
PCC	Pyridinium chlorochromate
PIFA	Bis(trifluoroacetoxy)iodobenzene
p-TsOH	p-Toluenesulfonic acid
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS-OTf	Trimethylsilyl trifluoromethanesulfonate
$(BOC)_2O$	Di-tert-butyl dicarbonate

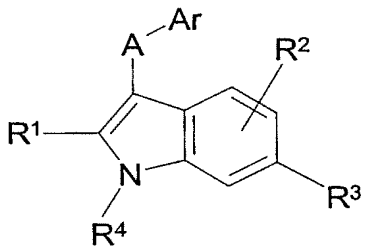
The naming and numbering of the compounds of this invention is illustrated below.



Formula I

In general, the nomenclature used in this Application is based on AUTONOM™ v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature.

Compounds of Formula I wherein R^1, R^2, R^3, R^4, A, and Ar are as defined below:



Formula I

Cpd #	R^1	R^2	R^4	R^3	A	Ar	MS. $[m+H]^+$
202	$-CH_3$	H	H	CH_3SO_2-	$-CH_2$-	4-fluoro-phenyl	318
401	$-CH_3$	H	H	CH_3SO_2-	-O-	4-fluoro-phenyl	320
101	$-CH_3$	H	H	CH_3SO_2-	-S-	4-fluoro-phenyl	336
212	$-CH_3$	H	H	CH_3SO_2-	$-CH_2$-	4-chloro-phenyl	335
201	$-CH_3$	H	H	CH_3SO_2-	$-CH_2$-	4-bromo-phenyl	379
106	$-CH_3$	H	H	CH_3SO_2-	-SO-	4-fluoro-phenyl	352
203	$-CH_3$	H	H	CH_3SO_2-	$-CH_2$-	3-fluoro-phenyl	318

102	$-CH_3$	H	H	CH_3SO_2-	-S-	4-methoxy-phenyl	348
103	$-CH_3$	H	H	CH_3SO_2-	-S-	4-chloro-phenyl	353
204	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	4-methoxy-phenyl	318
205	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	naphthalen-2-yl	350
402	$-CH_3$	H	H	CH_3SO_2-	-O-	2-chloro-4-methoxy-phenyl	367
403	$-CH_3$	H	H	CH_3SO_2-	-O-	2,4-difluoro-phenyl	338
404	$-CH_3$	H	H	CH_3SO_2-	-O-	2,4-dichloro-phenyl	371
405	$-CH_3$	H	H	CH_3SO_2-	-O-	4-chloro-phenyl	337
206	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	4-methyl-phenyl	314
207	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	4-trifluoro-methyl-phenyl	368
208	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	2,4-difluoro-phenyl	336
209	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	4-methyl-sulfanyl-phenyl	346
210	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	4-methoxy-naphthalen-1-yl	380
211	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	2-chloro-phenyl	335
104	$-CH_3$	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	354

105	$-CH_3$	H	H	CH_3SO_2-	-S-	2-chloro-4-fluoro-phenyl	371
213	$-CH_3$	H	H	CH_3SO_2-	$-CH_2-$	4-methane-sulfonyl-phenyl	378
502	$-CH_2OH$	H	H	CH_3SO_2-	-S-	4-fluoro-phenyl	352
302	-CN	H	H	CH_3SO_2-	-S-	4-fluoro-phenyl	347
301	-CN	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	365
303	-CN	H	H	CH_3SO_2-	-S-	4-methyl-phenyl	343
304	-CN	H	H	CH_3SO_2-	-S-	4-methoxy-phenyl	359
305	-CN	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	364
306	-CN	H	H	CH_3SO_2-	-S-	2-chloro-4-methoxy-phenyl	394
319	$-CONH_2$	H	H	CH_3SO_2-	-S-	4-fluoro-phenyl	365
318	$-CONH_2$	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	383
320	$-CONH_2$	H	H	CH_3SO_2-	-S-	4-methyl-phenyl	361
317	$-CONH_2$	H	H	CH_3SO_2-	-S-	4-methoxy-phenyl	377
315	$-CONH_2$	H	H	CH_3SO_2-	-S-	2-chloro-4-methoxy-phenyl	412
316	$-CONH_2$	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	382
307	-CN	H	H	CH_3SO_2-	-S-	4-chloro-phenyl	364

308	-CN	H	H	CH_3SO_2-	-S-	2-fluoro-4-methoxy-phenyl	377
309	-CN	H	H	CH_3SO_2-	-SO-	2,4-difluoro-phenyl	381
501	$-CH_2OH$	H	H	CH_3SO_2-	-S-	phenyl	334
601	$-CH_2SO_2CH_3$	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	431
801	-C(O)H	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	366
701	$-CH_2OC(O)CH_3$	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	411
321	-CON-nBu	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	439
322	-CON-iPr	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	425
327	-CONEt	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	411
323	$-CON(Me)_2$	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	411
324	$-CON(Et)_2$	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	439
325	-CON-nPr	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	425
326	-CONMe	H	H	CH_3SO_2-	-S-	2,4-difluoro-phenyl	397
311	-CN	H	H	CH_3SO_2-	-S-	4-ethoxy-phenyl	373
328	-CON-iPr	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	366
329	-CON-nBu	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	420
330	-CONEt	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	393

331	-CON-nPr	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	407
332	-CON-iPr	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	407
333	-CON-nBu	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	438
334	-CONEt	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	410
335	-CON(Et)$_2$	H	H	CH_3SO_2-	-S-	2-chloro-phenyl	438
336	-CONMe	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	379
337	-CON(Me)$_2$	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	393
338	-CON(Et)$_2$	H	H	CH_3SO_2-	-S-	2-fluoro-phenyl	421

While the broadest definition of this invention is shown above, certain compounds of Formula I are preferred.

In certain preferred embodiments Ar is a phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy, and R^3 is $-SO_2R^6$, wherein R^6 is alkyl.

Within the foregoing preferred embodiment, another preferred group of compounds is that wherein Ar is phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy; R^3 is $-SO_2R^6$, wherein R^6 is alkyl; A is -O-; and yet a more preferred group of compounds is that wherein Ar is phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy; R^3 is $-SO_2R^6$, wherein R^6 is alkyl; A is -O-; and R^1 is alkyl or cyano.

In another preferred embodiment a preferred group of compounds is that wherein Ar is phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy; R^3 is $-SO_2R^6$; wherein R^6 is alkyl; and A is -S-; and yet a more preferred group of compounds is that wherein Ar is phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy; R^3 is $-SO_2R^6$, wherein R^6 is alkyl; A is -S-; and R^1 is alkyl or cyano.

In another preferred embodiment a preferred group of compounds is that wherein Ar is phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy; R^3 is -SO_2R^6, wherein R^6 is alkyl; and A is -CH_2-; and yet a more preferred group of compounds is that wherein Ar is phenyl optionally substituted at one or more positions, preferably by one to two substitutents independently selected from the group consisting of halo and alkoxy; R^3 is -SO_2R^6, wherein R^6 is alkyl; A is -CH_2-; and R^1 is alkyl or cyano.

While the broadest definition of the invention is shown above, certain compounds of Formula I are preferred. For example, preferred compounds of Formula I are those in which R^1 is cyano or alkyl, R^2 is hydrogen or alkyl, R^3 is alkylsulfonyl, A is -S- or -O-, and Ar is unsubstituted, monosubstituted, or disubstituted phenyl. Even more preferred compounds of Formula I are those in which A is -S- or -O-, R^1 is cyano, R^2 is hydrogen, R^3 is alkylsulfonyl, and Ar is a phenyl mono or disubstituted with halo or alkoxy.

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, WI), Bachem (Torrance, CA), or Sigma (St. Louis, MO) or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-17 (John Wiley and Sons, 1991); *Rodd's Chemistry of Carbon Compounds*, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); *Organic Reactions*, Volumes 1-40 (John Wiley and Sons, 1991); *March's* Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and *Larock's* Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

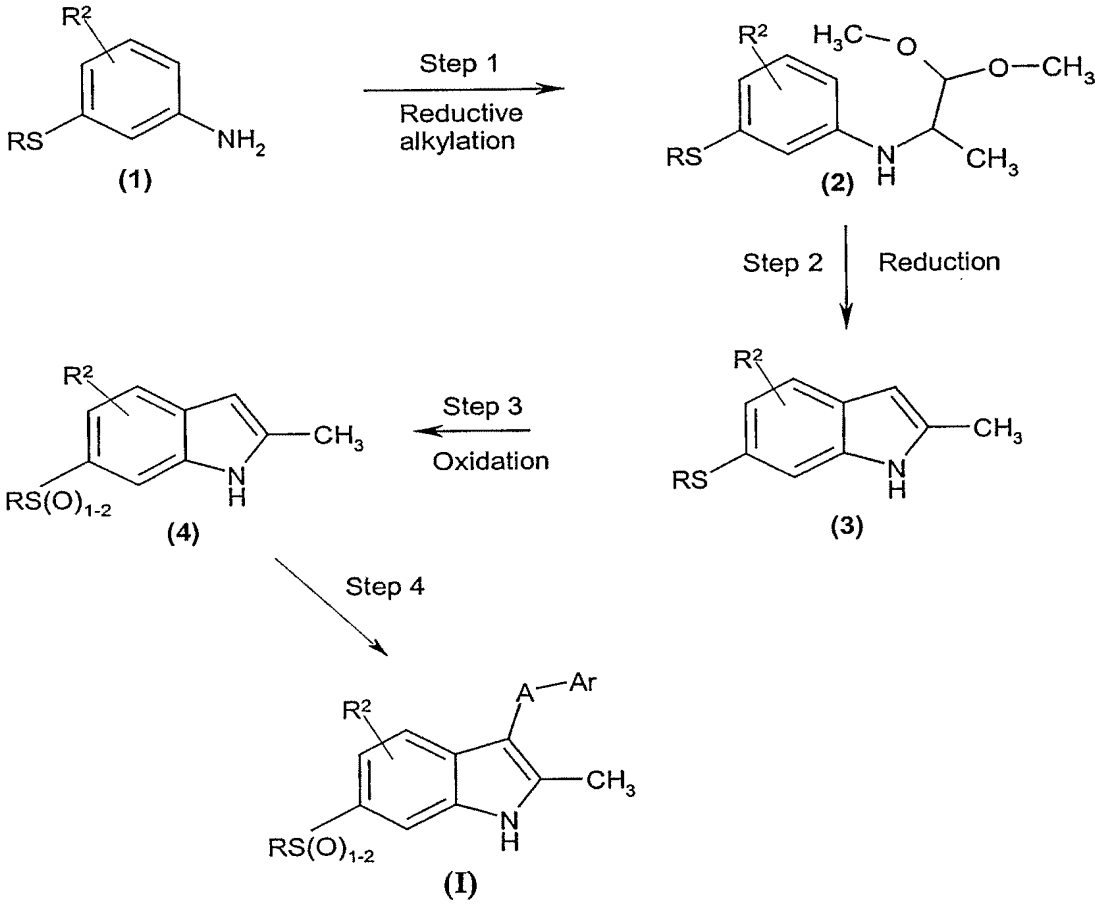
The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78°C to about 150°C, more preferably from about 0°C to about 125° C and most preferably at about room (or ambient) temperature, e.g., about 20°C.

A person of ordinary skill in the art will have no difficulty, having regard to that skill and this disclosure, in determining how to synthesize compounds of this invention.

Schemes A, B, and C, describe methods to prepare the compounds of Formula I.

Scheme A describes the synthesis of a compound of Formula I wherein A is -S- or -CH_2-; R^1 is methyl; R^4 is hydrogen; R^3 is $RS(O)_{1-2}$ (R is alkyl); and R^2 and Ar are as defined above.



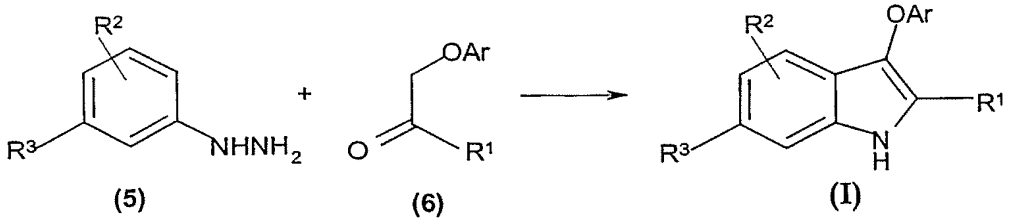
In Step 1, a certain alkylthioaniline of Formula (1), wherein R is alkyl, preferably wherein R is methyl, can undergo a reductive alkylation to give certain compounds of Formula (2). In general, the compounds of Formula (1) are commercially available or can be readily synthesized by those of ordinary skill in the art. For example, 3-methylsulfanyl-aniline can be prepared following the procedures described in Goldkamp, A.H.; *J. Org. Chem* ., 34, 6; (1969), 1780-1785.

In Step 2, a certain indole of Formula (3) wherein R is alkyl, preferably wherein R is methyl, can be prepared by methods known in the art. For example, 2-alkyl-6-alkylthioindoles can be prepared under reductive conditions following the procedures described in Allais, A., et al., *Eur. J. Med. Chem. – Chim. Ther.* 10(2) 187-99 (1975).

In Step 3, the -SR group of a certain compound of Formula (3) wherein R is alkyl, preferably wherein R is methyl, can be oxidized with for example MCPBA, OXONE ™, to provide a sulfoxide or a sulfone of Formula (4), wherein R is alkyl, preferably R is methyl. Suitable solvents for the reaction are alcohols (such as methanol and ethanol) or halogenated solvents (such as dichloromethane, chloroform). The sulfoxides of Formula (4) may be similarly converted to the corresponding sulfones. It is appreciated that this second oxidation may be performed at various points in Scheme A as may be required by the skilled artisan.

In Step 4, a certain sulfonylindole of Formula (4), wherein R is alkyl, preferably wherein R is methyl, can be coupled with a thiophenol of general formula ArSH by stirring in a suitable solvent, such as hexafluoroisopropanol, in the presence of PIFA to provide the compound of Formula (I) wherein A is -S-; or it can be treated with a benzaldehyde of general formula ArCHO in the presence of TMS-OTf in a suitable solvent, such as dichloromethane, followed by treatment with triethylsilane to provide the compound of Formula (I) wherein A is $-CH_2-$.

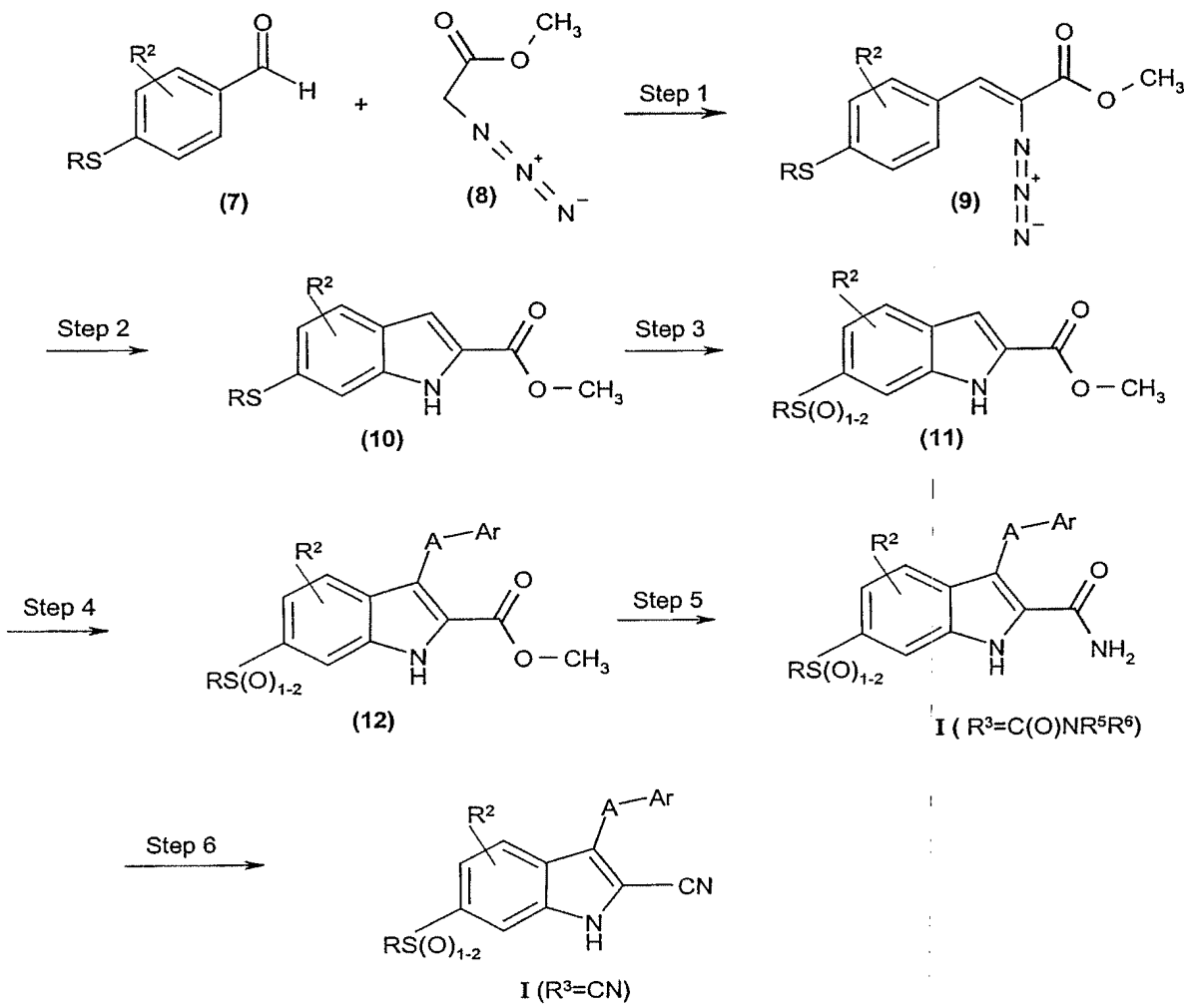
Scheme B describes the synthesis of a compound of Formula I wherein A is -O-, and R^1, R^2, R^3 and Ar are as defined above.



(5) (6) (I)

An indole of Formula (I) may be synthesized from certain compounds of Formula (5) and Formula (6) by methods known in the art. For example 2,3-diphenyl-1*H*-indole can be prepared following the procedures described in Baccolin, G.; et al.; *J Chem Soc, Chem Commun*, 1981, 11, 563.

Scheme C describes the synthesis of a compound of Formula I wherein A is -S- or $-CH_2-$, R^1 is -CN or $-C(O)NR^4R^5$, R^3 is $RS(O)_{1-2}$ (R is alkyl), and R^2 and Ar are as defined above.



In Step 1, a certain alkylthiobenzaldehyde, of Formula (7), can undergo a condensation with an azido-acetic acid ester of Formula (8), to form a certain compound of Formula (9). In general, the compounds of Formula (7) are commercially available or can be readily synthesized by those of ordinary skill in the art. For example, 4-mercapto-benzaldehyde can be prepared following the procedures described in Arnould, J. C.; et al.; *Tetrahedron Lett.*, 1996, 37(26), 4523-4524. In general the compounds of Formula (8) are commercially available or can be readily synthesized by those of ordinary skill in the art. For example 2-azido-propionic acid ethyl ester can be prepared by following the process described in Thomas, A. S.; et al.; *J Org Chem*, 1993, 58(22), 5886-5888.

In Step 2, an indole of Formula (10) can be prepared from a certain compound of Formula (9) by methods known in the art. For example 7-Bromo-4-methoxy-1*H*-indole-2-carboxylic acid methyl ester can be prepared following the procedures described in Semerth, S.; et al.; *J. Heterocycl. Chem.*, 1981, 18, 1373-1377.

In Step 3, the -SR group of a certain compound of Formula (10) wherein R is alkyl, preferably wherein R is methyl, can be oxidized with for example MCPBA, OXONE ™ to provide a sulfoxide or a sulfone of Formula (11), wherein R is alkyl, preferably R is methyl. Suitable solvents for the reaction are alcohols (such as methanol and ethanol) or halogenated solvents (such as dichloromethane, chloroform). Sulfoxides of Formula (11) may be similarly converted to the corresponding sulfones. It is appreciated that this second oxidation may be performed at various points in Scheme C as may be required by the skilled artisan.

In Step 4, a certain sulfonylindole of Formula (11), wherein R is alkyl, preferably wherein R is methyl, can be coupled with a thiophenol of general formula ArSH by stirring in a suitable solvent, such as hexafluoroisopropanol, in the presence of PIFA to provide the compound of Formula (12) wherein A is -S-; or it can be treated with a benzaldehyde of general formula ArCHO in the presence of TMS-OTf in a suitable solvent, such as dichloromethane, followed by treatment with triethylsilane to provide the compound of Formula (12) wherein A is $-CH_2-$.

In Step 5, a certain carboxylic acid of Formula (12) can undergo an amidation to give a certain compound of Formula (I). The above amidation can be performed by methods known in the art.

In Step 6, a certain amid of Formula (I) can be converted to a certain indolenitrile of Formula (I) by methods known in the art.

The compounds of the invention are inhibitors of prostaglandin G/H Synthase I and II (COX-I and COX-II), especially COX-II, *in vitro*, and as such are expected to possess both anti-inflammatory and analgesic properties *in vivo*. See, for example, Goodman and Gilmans's "The Pharmacological Basis of Therapeutics", Ninth Edition, McGraw Hill, New York, 1996, Chapter 27. The compounds, and compositions containing them, are therefore useful as anti-inflammatory and analgesic agents in mammals, especially humans. They find utility in the treatment of fever, inflammation, and pain caused by conditions such as rheumatic fever, symptoms associated with influenza or other viral infections, low back and neck pain, dysmenorrhoea, headache, dental pain, sprains, strains, sports injuries, bursitis, tendonitis, myositis, synovitis, arthritis (rheumatoid arthritis and osteoarthritis), gout, ankylosing spondylitis, burns, or injuries. They maybe used to inhibit prostanoid-induced smooth muscle contractions (e.g., in the treatment of dysmenorrhoea, premature labor, and asthma) and to treat autoimmune disorders (such as systemic lupus erythematosus and type I diabetes).

As inhibitors of prostaglandin G/H Synthase, the compounds of this invention are also expected to be useful in the prevention and treatment of cancer, in particular colon cancer. It has been shown that COX-II gene expression is upregulated in human colorectal cancers and that drugs that inhibit prostaglandin G/H Synthase are effective in animal models of cancer (Eberhart, C.E., *et. al.*, *Gastroenterology*, 107, 1183-1188, (1994); and Ara, G. and Teicher, B.A., *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 54, 3-16, (1996)). In addition, there is epidemiological evidence that shows a correlation between use of drugs that inhibit prostaglandin G/H synthase and a reduced risk of developing colorectal cancer, (Heath, C.W. Jr., *et. al.*, *Cancer*, 74, No. 10, 2885-8, (1994)).

The compounds of this invention are also expected to be useful in the prevention and treatment of Alzheimer's disease. Indomethacin, an inhibitor of prostaglandin G/H synthase, has been shown to inhibit the cognitive decline of Alzheimer's patients, (Rogers, J., *et. al.*, *Neurology*, 43, 1609, (1993)). Also, the use of drugs which inhibit prostaglandin G/H synthase has been linked epidemiologically with a delayed onset of Alzheimer's disease, (Breitner, J.C.S., *et. al.*, *Neurobiology of Aging*, 16, No. 4, 523, (1995) and *Neurology*, 44, 2073, (1994)).

The anti-inflammatory activity of the compounds of this invention may be assayed by measuring the ability of the compound to inhibit COX-I and COX-II, especially COX-II, *in vitro*, using a radiometric assay, as described in more detail in Example 10. It may also be assayed by *in vivo* assays such as the Rat Carrageenan Paw and Rat Air-Pouch assays, as described in more detail in Examples 11 and 12 The analgesic activity of the compounds of this invention may be assayed by *in vivo* assays such as the Randall-Selitto assay and the rat arthritis pain model, as described in Example 13.

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of Formula I may range from approximately 0.005-10 mg per kilogram body weight of the recipient per day; preferably about 0.05-1 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would preferably be about 3.5 mg to 400 mg per day.

In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal,

intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

The compositions are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula I. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art .

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol, and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

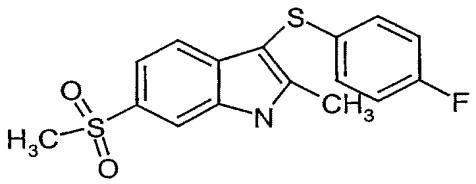
Other suitable pharmaceutical excipients and their formulations are described in *Remington's Pharmaceutical Sciences*, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-99.99 wt% of a compound of Formula V based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt%. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 7.

EXAMPLES

Example 1

3-(4-Fluoro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole



Step 1:

Preparation of 2-methyl-6-methylsulfanyl-indole-1-carboxylic acid *tert*-butyl ester

2-Methyl-6-methylthioindole (13.9 g) prepared according to Allais A. et al. *Eur. J. Med. Chem. - Chim. Ther.* (1975), 10(2), 187-99, was dissolved in CH_3CN (150 ml) followed by the addition of $(BOC)_2O$ (18 g) with 480 mg DMAP. After 5 hours the mixture was evaporated to dryness and the resulting 2-methyl-6-methylsulfanyl-indole-1-carboxylic acid *tert*-butyl ester was purified by chromatography over silica gel.

Step 2:

Preparation of 6-methanesulfonyl-2-methyl-indole-1-carboxylic acid *tert*-butyl ester

The product of step 1 (20.3 g) was treated with 135 g OXONE™ in 300 ml 1:1 MeOH/water for 2 hours. The mixture was partitioned between methylene chloride and water, the organic layer was separated, washed, dried, and evaporated to dryness to yield 6-methanesulfonyl-2-methyl-indole-1-carboxylic acid *tert*-butyl ester (16 g) as a solid.

Step 3:

Preparation of 6-methanesulfonyl-2-methyl-1*H*-indole

The above product of step 2 was dissolved in 100 ml methylene chloride and treated with 12 ml TFA. After stirring overnight, the volatiles were removed and the product crystallized from 10:1 methylene chloride/MeOH. In this way 8.0 g of 6-methanesulfonyl-2-methyl-1*H*-indole was obtained.

Step 4:

Preparation of 3-(4-fluoro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole

A solution of 6-methanesulfonyl-2-methyl-1*H*-indole (207 mg, 1 mmol) in 6 ml of hexafluoroisopropanol was treated with 4-fluorothiophenol (2 mmol) followed by addition of PIFA (1.5 mmol). The dark colored solution was stirred for 30 minutes followed by partitioning between EtOAc and water. Purification by TLC (2:1 hexane/EtOAc) afforded 145 mg of 3-(4-fluoro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole, 101, MS: 336 ($[M+H]^+$).

Similarly, following the procedure described above in Step 4, but replacing 4-fluorothiophenol with the appropriately substituted thiophenol the additional compounds of Formula I wherein A is -S- , were prepared:

6-methanesulfonyl-3-(4-methoxy-phenylsulfanyl)-2-methyl-1*H*-indole, 102, MS: 348 ($[M+H]^+$);

3-(4-chloro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole, 103, MS: 353 ($[M+H]^+$);

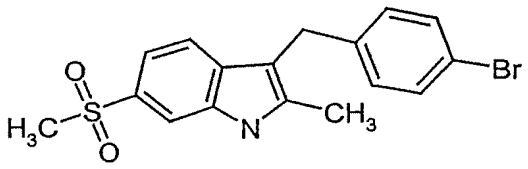
3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole, 104, MS: 354 ($[M+H]^+$); and

3-(2-chloro-4-fluoro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole, 105, MS: 371 ($[M+H]^+$).

Oxidation of 3-(4-fluoro-phenylsulfanyl)-6-methanesulfonyl-2-methyl-1*H*-indole, 101 with one equivalent of Oxone™, yielded 3-(4-Fluoro-benzenesulfinyl)-6-methanesulfonyl-2-methyl-1*H*-indole 106, MS: 352 ($[M+H]^+$)

Example 2

3-(4-Bromo-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole



A solution of 6-methanesulfonyl-2-methyl-1*H*-indole (112 mg), prepared as described in Example 1 Step 3, in 9 ml CH_2Cl_2 was treated with p-bromobenzaldehyde (100 mg) and 0.2 ml TMS-OTf. After cooling to 0 °C, 0.26 ml of Et_3SiH was added. The solution was stirred for 30 minutes followed by partitioning between EtOAc and water. Purification by TLC (2:1 hexane/EtOAc) gave 130 mg of 3-(4-bromo-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole 201, MS: 379 ($[M+H]^+$).

Similarly, following the procedure described above, but replacing p-bromobenzaldehyde with the appropriately substituted benzaldehyde, the additional compounds of Formula I wherein A is -C- , were prepared:

3-(4-Fluoro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole 202, MS: 318 ($[M+H]^+$);

3-(3-Fluoro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole 203, MS: 318 ($[M+H]^+$);

6-Methanesulfonyl-3-(4-methoxy-benzyl)-2-methyl-1*H*-indole 204, MS: 318 ($[M+H]^+$);

6-Methanesulfonyl-2-methyl-3-naphthalen-2-ylmethyl-1*H*-indole 205, MS: 350 ($[M+H]^+$);

6-Methanesulfonyl-2-methyl-3-(4-methyl-benzyl)-1*H*-indole 206, MS: 314 ($[M+H]^+$);

6-Methanesulfonyl-2-methyl-3-(4-trifluoromethyl-benzyl)-1*H*-indole; 207, MS: 368 ($[M+H]^+$);

3-(2,4-Difluoro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole 208, MS: 336 ($[M+H]^+$);

6-Methanesulfonyl-2-methyl-3-(4-methylsulfanyl-benzyl)-1*H*-indole 209, MS: 346 ($[M+H]^+$);

6-Methanesulfonyl-3-(4-methoxy-naphthalen-1-ylmethyl)-2-methyl-1*H*-indole 210, MS: 380 ($[M+H]^+$);

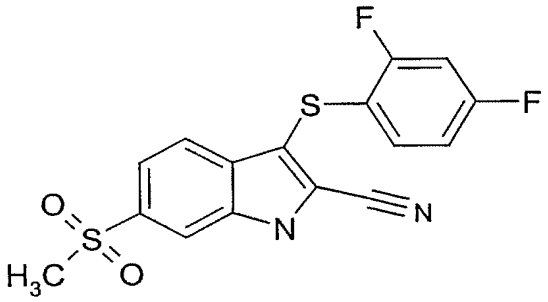
3-(2-Chloro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole 211, MS: 335 ($[M+H]^+$);

3-(4-Chloro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole 212, MS: 335 ($[M+H]^+$); and

6-Methanesulfonyl-2-methyl-3-(4-methylsulfonyl-benzyl)-1*H*-indole 213, MS: 378 ($[M+H]^+$).

Example 3

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile



Step 1:

Preparation of 2-carbomethoxy-6-methanesulfonylindole

Sodium (16.6 g) was dissolved in 600 ml MeOH and cooled to –20 °C. A mixture of methyl diazoacetate (83.2 g), 4-thiomethylbenzaldehyde, and 30 ml MeOH was added dropwise over 45 min. After stirring 3 hours at –20 °C the mixture was kept at 0 °C in the refrigerator for two days. The material was partitioned between EtOAc and water to remove a large quantity of solid polymer. After drying and solvent removal the crude azidoester was dissolved in 700 ml toluene and refluxed for 3 hours. The solvent was removed and the resulting 2-carbomethoxy-6-methylthioindole was purified by flash chromatography. The product was then dissolved in 200 ml MeOH and 100 ml THF. OXONE™ (3 eq) in 100 ml water was added and the reaction was stirred for 2 hours at room temperature. The mixture was partitioned between CH_2Cl_2 and water. The product, 2-carbomethoxy-6-methanesulfonylindole, was obtained as a white solid upon evaporation of the organic phase (16.0 g).

Step 2:

Preparation of 3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid methyl ester

A solution of 2-carbomethoxy-6-methanesulfonylindole (750 mg, 2.8 mmol), in 10 ml hexafluoroisopropanol was treated with 2,4-difluorothiophenol (7.5 mmol) followed by addition of PIFA (5.6 mmol). The dark colored solution was stirred overnight then partitioned between methylene chloride and water. After concentration of the methylene chloride layer to 20 ml the product was precipitated by addition of 30 ml hexane. An 88 %

yield of 3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid methyl ester was obtained.

Step 3:

Preparation of 3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid amide

The product from step 2 was stirred for 36 hours with 4.5 eq LiOH in 12 ml 1:1 water/THF. The mixture was partitioned between EtOAc and 2N HCl to obtain the crude acid. This material (452 mg) was dissolved in 8 ml benzene and 3 ml methylene chloride, and treated with 0.16 ml oxalyl chloride and a catalytic amount of DMF. After stirring 14 hours, 10 ml 0.5M NH_3 in dioxane was added. After stirring 3 hours the mixture was partitioned between water and methylene chloride. The product was purified by TLC (5 % MeOH/methylene chloride). The yield of 3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid amide was 427 mg.

Step 4:

Preparation of The 3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile

The amide, of step 3, (250 mg) was dissolved in 8 ml dioxane and treated with TFA-anhydride (0.28 ml) and pyridine (0.4 ml). After 6 hours the reaction was concentrated and purified by TLC (3 % MeOH/methylene chloride). The 3-(2,4-difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile 301 (220 mg) was obtained as a solid, MS: 365 ($[M+H]^+$).

Similarly, following the procedure described above in step 2, but replacing 2,4-difluorothiophenol with the appropriate substituted thiophenol the additional compounds of Formula I wherein A is -S-, were prepared:

3-(4-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile, 302, MS: 347 ($[M+H]^+$);

6-Methanesulfonyl-3-*p*-tolylsulfanyl-1*H*-indole-2-carbonitrile, 303, MS: 343 ($[M+H]^+$);

6-Methanesulfonyl-3-(4-methoxy-phenylsulfanyl)-1*H*-indole-2-carbonitrile, 304, MS: 365 ($[M+H]^+$);

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile, 305, MS: 364 ([M+H]$^+$);

3-(2-Chloro-4-methoxy-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile, 306, MS: 394 ([M+H]$^+$);

3-(4-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile, 307, MS: 364 ([M+H]$^+$);

3-(2-Fluoro-4-methoxy-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile, 308, MS: 377 ([M+H]$^+$);

3-(2,4-Difluoro-benzenesulfinyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile, 309, MS: 381 ([M+H]$^+$);

6-Methanesulfonyl-3-(4-ethoxy-benzyl)-1*H*-indole-2-carbonitrile, 311, MS: 373 ([M+H]$^+$)

Similarly, following the procedure described above in Step 2, but replacing 2,4-difluorothiophenol with the appropriate substituted thiophenol, and omitting Step 4 the additional compounds of Formula I wherein A is -S-, were prepared:

3-(2-Chloro-4-methoxy-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid amide, 315, MS: 412 ([M+H]$^+$);

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid amide, 316, MS: 382 ([M+H]$^+$);

6-Methanesulfonyl-3-(4-methoxy-phenylsulfanyl)-1*H*-indole-2-carboxylic acid amide, 317, MS: 377 ([M+H]$^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid amide, 318, MS: 383 ([M+H]$^+$);

3-(4-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid amide, 319, MS: 382 ([M+H]$^+$); and

6-Methanesulfonyl-3-*p*-tolylsulfanyl-1*H*-indole-2-carboxylic acid amide, 320, MS: 382 ([M+H]$^+$).

Similarly, following the procedure described above in Step 2, but replacing 2,4-difluorothiophenol with the appropriate substituted thiophenol followed by alkylation of

the amide obtained in Step 3 by methods known to those skilled in the art, the additional compounds of Formula I wherein A is -S-, were prepared:

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid butylamide, 321, MS: 439 ($[M+H]^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid isopropylamide, 322, MS: 425 ($[M+H]^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid dimethylamide, 323, MS: 411 ($[M+H]^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid diethylamide, 324, MS: 439 ($[M+H]^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid propylamide, 325, MS: 425 ($[M+H]^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid methylamide, 326, MS: 397 ($[M+H]^+$);

3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid ethylamide, 327, MS: 411 ($[M+H]^+$);

3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid isopropylamide, 328, MS: 366 ($[M+H]^+$);

3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid butylamide, 329, MS: 420 ($[M+H]^+$);

3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid ethylamide, 330, MS: 393 ($[M+H]^+$);

3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid propylamide, 331, MS: 407 ($[M+H]^+$);

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid isopropylamide, 332, MS: 407 ($[M+H]^+$);

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid butylamide, 333, MS: 438 ($[M+H]^+$);

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid ethylamide, 334, MS: 410 ($[M+H]^+$);

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid diethylamide, 335, MS: 438 ($[M+H]^+$);

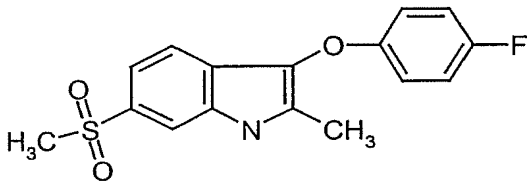
3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid methylamide, 336, MS: 379 ($[M+H]^+$);

3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid dimethylamide, 337, MS: 393 ($[M+H]^+$); and

3-(2-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid diethylamide, 338, MS: 421 ($[M+H]^+$).

Example 4

3-(4-Fluoro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole



Step 1:

Preparation of 1-(4-fluoro-phenoxy)-propan-2-one

To a mixture of para-fluorophenol (15 g) and K_2CO_3 (18.5 g) in 100 ml acetone were added chloroacetone (10.4 ml) and of KI (22 g). After heating at reflux for 18 hours the reaction mixture was cooled down and left at room temperature overnight. The reaction mixture was filtered, washed with acetone, and evaporated to dryness. The residue was partitioned between dichloromethane and water, the organic layer was separated and washed with water, dried over $MgSO_4$, and evaporated to yield 15 g of 1-(4-fluoro-phenoxy)-propan-2-one as a yellow liquid.

Step 2:

Preparation of (3-methanesulfonyl-phenyl)-hydrazine

To a solution of 3-methanesulphonyl-phenylamine (2.5 g) in 6 ml HCl was added a solution of $NaNO_2$ in 5 ml of H_2O at –5 °C to 0 °C. After stirring for 30 min the resulted

diazonium salt was poured into a cold solution (-10 ° C to -15 °C) of stannous chloride in 6 ml HCl. The mixture of resulted hydrazine hydrochloride in HCl was stored in the refrigerator overnight. The solution was basified to pH 10, by addition of a 6N solution of NaOH, and extracted with THF. The organic layer was washed, dried over $MgSO_4$, and evaporated to yield 2 g of a light brown solid (3-methanesulfonyl-phenyl)-hydrazine.

Step 3:

3-(4-Fluoro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole

To the solution of (3-methanesulfonyl-phenyl)-hydrazine (1.35 g) and 1-(4-fluoro-phenoxy)-propan-2-one (1.01 g) in benzene at room temperature was added equimolar amount of PCl_3. The reaction mixture was stirred at room temperature for 1 hour and the solvent was removed *in vacuo*. The residue was purified by Biotage chromatography, eluted with 10-30 % EtOAc/Hexane to yield 0.1 g of 3-(4-fluoro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole 401 as a light orange powder, MS: 320 ($[M+H]^+$).

Similarly, following the procedure in Step 3 described above, but replacing 1-(4-fluoro-phenoxy)-propan-2-one with the appropriately substituted phenoxy-propane-2-one the additional compounds of Formula I wherein A is -O- were prepared:

3-(2-Chloro-4-methoxy-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole, 402, MS: 366 ($[M+H]^+$);

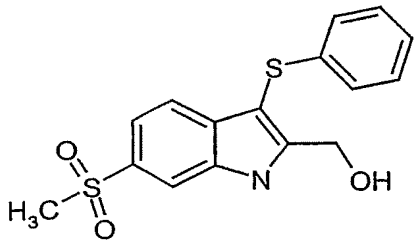
3-(2,4-Difluoro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole, 403, MS: 377 ($[M+H]^+$);

3-(2,4-Dichloro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole 404, MS: 370 ($[M+H]^+$);

3-(4-Chloro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole 405, MS: 336 ($[M+H]^+$).

Example 5

(6-Methanesulfonyl-3-phenylsulfanyl-1*H*-indol-2-yl)-methanol

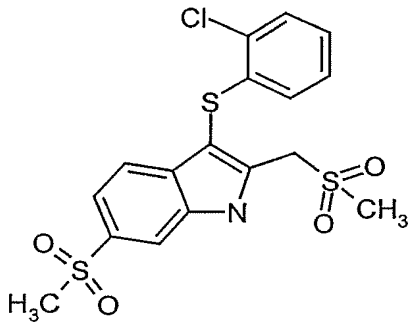


A solution of (6-methanesulfonyl-3-phenylsulfanyl-1*H*-indol-2-yl)-2-carboxylic acid methyl ester (800 mg), prepared as in Example 3, Steps 1 and 2, in THF (35 ml) was treated with 5.6 ml 1.5M DIBAL in toluene at -78 °C, then allowed to warm to room temperature over 30 minutes. It was poured into 3N HCl and extracted with EtOAc. The product was purified by SiO_2 chromatography (eluting with 30 % EtOAc/hexane) to yield 686 mg of (6-methanesulfonyl-3-phenylsulfanyl-1*H*-indol-2-yl)-methanol 501, MS: 334 ($[M+H]^+$).

Similarly, following the procedure described above [3-(4-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indol-2-yl]-methanol 502 , MS: 352 ($[M+H]^+$) was prepared.

Example 6

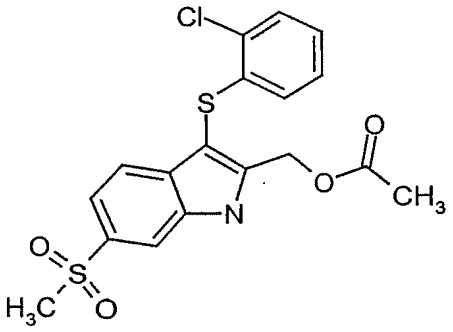
3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-2-methanesulfonylmethyl-1*H*-indole



[3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indol-2-yl]-methanol (1 mmole) (as prepared in Example 5) was dissolved in 2 ml CH_2Cl_2 and treated with 0.3 ml NEt_3 followed by 0.08 ml MsCl. After stirring 10 min. 3 ml DMF was added followed by 0.5 g $NaSO_2Me$. The mixture was stirred overnight. The reaction mixture was evaporated to dryness and applied to a PTLC plate. Elution with 1:1 EtOAc/hexane gave 80 mg 3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-2-methanesulfonylmethyl-1*H*-indole 601, MS: 343 ($[M+H]^+$).

Example 7

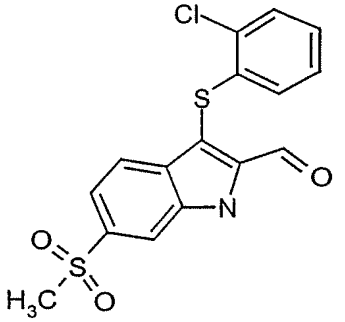
Acetic acid 3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indol-2-yl methyl ester



A solution of [3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indol-2-yl]-methanol (75 mg) (prepared as described in example 5) in pyridine (2 ml) was treated with 0.5 ml Ac_2O. After 30 min. all volatiles were removed to yield 82 mg of acetic acid 3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indol-2-yl methyl ester 701, MS: 411 ($[M+H]^+$).

Example 8

3-(2-Chloro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbaldehyde



A solution of alcohol [3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-1H-indol-2-yl]-methanol (75 mg) (prepared as described in Example 5) in CH_2Cl_2 (5 ml) was added to a solution of DMSO (0.2 ml) and oxalyl chloride (0.1 ml) that had been prepared at –78°. After 15 min triethylamine (.45 ml) was added and the reaction was allowed to warm to 20° over 30 min. It was partitioned between EtOAc and water and the organic phase evaporated to give3-(2-chloro-phenylsulfanyl)-6-methanesulfonyl-1H-indole-2-carboxaldehyde, 801, MS: 343 ($[M+H]^+$).

Example 9

The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0g
fumaric acid	0.5g
sodium chloride	2.0g
methyl paraben	0.15g
propyl paraben	0.05g
granulated sugar	25.5g
sorbitol (70% solution)	12.85g
Veegum K (Vanderbilt Co.)	1.0g
flavoring	0.035ml
colorings	0.5mg
distilled water	q.s. to 100 ml

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	0.4 mg
sodium acetate buffer solution, 0.4 M	2.0 ml
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 ml

Example 10

Inhibition of COX-I and COX-II *in vitro*

The COX-I and COX-II inhibitory activity of compounds of this invention *in vitro* was determined using partially purified COX-I and COX-II enzymes, prepared as described in J. Barnett *et. al.*, *Biochim. Biophys. Acta*, 1209, 130-139 (1994).

COX-I and COX-II samples were diluted with Tris-HCl buffer (50 mM Tris-HCl, pH 7.9) containing 2 mM EDTA and 10 % glycerol and reconstituted by incubating first with 2 mM phenol for 5 minutes and then with 1 micromolar hematin for an additional 5

minutes. 125 µl of the reconstituted COX-I or COX-II enzyme were preincubated for 10 minutes at room temperature in a shaking water bath with the compounds of the invention dissolved in 2-15 µl of DMSO or the carrier vehicles (control samples). The enzyme reaction was initiated by adding 25 µl of 1-[14 C] arachidonic acid (80,000-100,000 cpm/tube; 20 micromolar final concentration) and the reaction was allowed to continue for an additional 45 seconds. The reaction was terminated by adding 100 µl of 2N HCl and 750 µl water. An aliquot (950 µl) of the reaction mixture was loaded onto a 1 ml C_{18} Sep-Pak column (J.T. Baker, Phillipsburg, NJ) which had been previously washed with 2-3 ml methanol and equilibrated with 5-6 ml distilled water. Oxygenated products were quantitatively eluted with 3 ml of acetonitrile/water/acetic acid (50:50:0.1, v/v) and the radioactivity in the eluate determined in a scintillation counter.Compounds of this invention were active in this assay for COX-II.

The COX inhibitory activities (expressed as IC_{50}, the concentration causing 50% inhibition of the COX enzyme being assayed) of some exemplary compounds of the invention were:

CPD #	COX-I IC_{50}	COX-II IC_{50}
204	7.3	5.09
405	11.5	3.83
105	21.6	3.03

Example 11

Anti-inflammatory activity

The anti-inflammatory activity of compounds of this invention was determined by measuring the inhibition of carrageenan-induced paw edema in the rat, using a modification of the method described in Winter C. A. *et al.*, "Carrageenan-Induced Edema in Hind Paw of the Rat as an Assay for Anti-inflammatory Drugs" *Proc. Soc. Exp. Biol. Med.* 111, 544-547, (1962). This assay has been used as a primary *in vivo* screen for anti-inflammatory activity of most NSAIDs, and is considered predictive of human efficacy. Briefly, test materials were administered orally to female rats in a volume of 1 ml prepared as solutions or suspensions in an aqueous vehicle containing 0.9 % sodium chloride, 0.5 % sodium carboxymethyl-cellulose, 0.4 % polysorbate 80, 0.9 % benzyl alcohol, and 97.3

% distilled water. Control rats received vehicle alone. After 1 hour 0.05 ml of a 0.5 % solution of Carrageenan (Type IV Lambda, Sigma Chemical Co.) in 0.9 % saline was injected into the subplantar region of the right hind paw. Three hours later the rats were euthanized in a carbon dioxide atmosphere; hind paws were removed by severing at the tatso-crural joint; and the left and right paws were weighed. The increase in weight of the right paw over the left paw was obtained for each animal and the mean increases were calculated for each group. The anti-inflammatory activity of the test materials is expressed as the percent inhibition of the increase in hind paw weight of the test group relative to the vehicle dosed control group.

Compounds of this invention were active in this assay.

Example 12

Inhibition of eicosanoid synthesis *in vivo*

The activity of compounds of this invention in inhibiting *in vivo* eicosanoid (prostaglandin E_2) synthesis in inflamed tissues was determined by the carrageenan-induced inflammation (air-pouch model) in rats, using a modification of the method described in Futaki, M., *et al.*, "Selective Inhibition of NS-398 on prostanoid production in inflamed tissue in rat Carrageenan Air-pouch Inflammation" *J. Pharm. Pharmacol.* 45, 753-755, (1993) and Masferrer, J. L., *et al.*; "Selective Inhibition of inducible cyclooxygenase 2 *in vivo* is Antiflammatory and Nonulcerogenic" *Proc. Natl. Acad. Sci. USA.* 91, 3228-3232, (1994). In this assay, an air-pouch is created in the rat and the PGE_2 levels in the air-pouch exudate are measured by enzyme immunoassay. Briefly, male rats were anesthetized using a 60:40 CO_2:O_2 mixture and subsequently injected subcutaneously with 20 ml of sterilized air, under aseptic conditions, in the proximal area of the dorsum. This injection of sterile air causes the creation of a subcutaneous "air pouch". The next day, a further 10 ml of sterile air was injected into the previously formed pouch using the same technique. The test materials were administered orally in a volume of 1 ml/100 g body weight as solutions or suspensions in an aqueous vehicle containing 0.9 % sodium chloride, 0.5 % sodium carboxymethyl-cellulose, 0.4 % polysorbate 80, 0.9 % benzyl alcohol, and 97.3 % water. Control rats received vehicle alone. After 30 minutes, 5 ml of a 0.5 % solution of carrageenan (Sigma, Lambda Type IV) was injected into the air pouch. The rats were euthanized 3 or 6 hours after the compound administration. 10 ml of a solution containing 10 µg/l of indomethacin and 5.4 mM EDTA in 0.9 % sterile saline was injected into the air pouch; the air pouch was cut open; and the exudate was harvested. The total exudate volume was recorded, and the samples were analyzed for PGE_2 and 6-keto PGF_1 by ELISA (Titerzyme ®, PerSeptive Diagnostics, Boston, MA) and TxB_2 by radioimmuno assay (New England Nuclear Research, Boston MA, Catalog No. NEK-037), according to the manufacturer's directions.

The mean concentrations of PGE_2 were calculated for each group. The anti-inflammatory activity of test materials is expressed as the percent inhibition of PGE_2 formation in the test group relative to the control group.

Compounds of this invention were active in this assay.

Example 13

Analgesic Activity

The analgesic activity of the compounds of this invention may be determined by using a modification of the method described in Randall, L. O., and Selitto, J. J., "A Method for Measurement of Analgesic Activity on Inflamed Tissue", *Arch. Int. Pharmacodyn.*, CXI, 4, 409, (1957) and Gans, *et. al.*, " Anti-Inflammatory and Safety Profile of DuP 697, a Novel Orally Effective Prostaglandin Synthesis Inhibitor", *J. Pharmcol. Exp. Ther.*, 254, No. 1, 180, (1990). In this assay, the male Sprague Dawley rats were injected with 0.1 ml of 20 % brewer's yeast in deionized water (Sigma, St. Louis) in the subplantar region of the left hind foot. After 2 hours, the test materials were administered orally in a volume of 1 ml/100 g body weight as solutions or suspensions in an aqueous vehicle containing 0.9 % sodium chloride, 0.5 % sodium carboxymethyl-cellulose, 0.4 % polysorbate 80, 0.9 % benzyl alcohol, and 97.3 % water. Control rats received vehicle alone. After 1 hour, the hindpaw was placed on the platform of a Basile Analgesy-Meter (Ugo Biological Research Apparatus, Italy, Model # 7200) and mechanical force was applied to the dorsum of the rat's hindpaw. Compounds of the invention were active in this assay.

The analgesic activity of compounds of this invention may also be determined by using an adjuvant-induced arthritis pain model in the rat, where pain is assessed by the animal's vocal response to the squeezing or flexing of an inflamed ankle joint, as described in Winter C.A. and Nuss, G.W., "Treatment of Adjuvant Arthritis in rats with Anti-inflammatory Drugs", *Arthritis Rheum.*, 9, 394-403, (1966) and Winter, C.A., Kling P.J., Tocco, D.J., and Tanabe, K., "Analgesic activity of Diflunisal [MK-647; 5-(2,4-Difluorophenyl)salicylic acid] in Rats with Hyperalgesia Induced by Freund's Adjuvant", *J. Pharmacol. Exp. Ther.*, 211, 678-685, (1979).

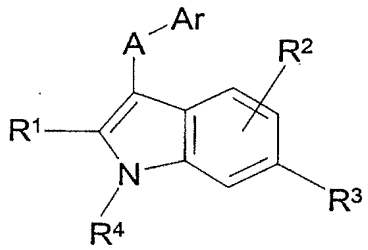
The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined

with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

Claims

1. A compound selected from the group of compounds represented by Formula I



wherein:

A is a $-CH_2-$, -O-, -S-, or -S(O)-;

Ar is an optionally substituted phenyl or an optionally substituted naphthalenyl;

R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkylthio, halo, cyano, $-C(O)R^5$, $-C(O)NR^5R^6$, $-NR^5R^6$, $-(CR'R'')_{0-3}OC(O)R^5$, $-(CR'R'')_{0-3}SO_2R^5$, and $-(CR'R'')_{0-3}NSO_2R^5$, wherein R^5, R^6, R' and R'' are each independently in each occurrence hydrogen or C_{1-6} alkyl, with the proviso that when A is $-CH_2-$, then R^1 is not $-C(O)NR^5R^6$;

R^2 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halo, halo C_{1-6} alkyl, nitro, cyano, or $-NR^5R^6$, wherein R^5 and R^6 are as defined previously;

R^3 is $-SOR^7$, $-SO_2R^7$, or $-SO_2NR^5R^6$ wherein R^7 is C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, or C_{1-6} alkoxycarbonyl C_{1-6} alkyl; and R^5 and R^6 are as defined previously;

R^4 is hydrogen or C_{1-6} alkyl;

or individual isomers, mixtures of isomers, or pharmaceutically acceptable salts thereof.

2.The compound according to claim 1 wherein:

A is a $-CH_2-$, -O-, -S-, or -S(O)-;

Ar is an optionally substituted phenyl;

R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkylthio, halo, cyano, $-C(O)NR^5R^6$, $-NR^5R^6$, $-(CR'R'')_{0-3}OC(O)R^5$, $-(CR'R'')_{0-3}SO_2R^5$, and $-(CR'R'')_{0-3}NSO_2R^5$, wherein R^5, R^6, R' and R'' are each independently in each occurrence hydrogen or C_{1-6} alkyl, with the proviso that when A is $-CH_2-$, then R^1 is not $-C(O)NR^5R^6$;

R^2 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halo, halo C_{1-6} alkyl, nitro, cyano, or $-NR^5R^6$, wherein R^5 and R^6 are as defined previously;

R^3 is $-SOR^7$, $-SO_2R^7$, or $-SO_2NR^5R^6$ wherein R^7 is C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, or C_{1-6} alkoxycarbonyl C_{1-6} alkyl; and R^5 and R^6 are as defined previously;

R^4 is hydrogen or C_{1-6} alkyl.

3. The compound according to claims 1 or 2 wherein Ar is phenyl optionally substituted at one or two substitutents independently selected from the group consisting of halo and C_{1-6} alkoxy, and R^3 is $-SO_2R^7$, wherein R^7 is C_{1-6} alkyl.

4. The compound according to claims 1, 2 or 3 wherein A is -O-.

5. The compound according to any one of claims 1 to 4 wherein R^1is C_{1-6} alkyl or cyano.

6. The compound according to claims 1, 2 or 3 wherein A is -S-.

7. The compound according to any one of claims 1, 2, 3 and 6 wherein R^1 is C_{1-6} alkyl, hydroxy C_{1-6} alkyl, or cyano.

8. The compound according to claims 1, 2 or 3 wherein A is $-CH_2-$.

9. The compound according to any one of claims 1, 2, 3 and 8 wherein R^1 is C_{1-6} alkyl or cyano.

10. The compound according to claim 1 comprising:

3-(2-Chloro-benzyl)-6-methanesulfonyl-2-methyl-1*H*-indole;
(6-Methanesulfonyl-3-phenylsulfanyl-1*H*-indol-2-yl)-methanol;
3-(4-Fluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile;
3-(2,4-Difluoro-phenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carbonitrile;
3-(4-Fluoro-benzenesulfinyl)-6-methanesulfonyl-2-methyl-1*H*-indole;
3-(4-Fluoro-phenoxy)-6-methanesulfonyl-2-methyl-1*H*-indole.

11. A medicament comprising a therapeutically effective amount of a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable excipient.

12. Compounds according to any one of claims 1 to 10 for use as therapeutically active substances.

13. Use of a compound according to any one of claims 1 to 10 for the manufacture of medicaments comprising one or more compounds according to any one of claims 1 to 10 for the treatment of disease treatable by selective COX II inhibitor.

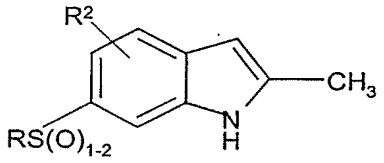
14. The use according to claim 13, wherein the disease is an inflammatory disease selected from myositis, synovitis, arthritis (rheumatoid arthritis and osteoarthritis), gout, back pain, dental pain, sports injuries, sprains, strains, headache, tendonitis, ankylosing, sponylitis and bursitis.

15. The use according to claim 13, wherein the disease is dysmenorrhoea or premature labor.

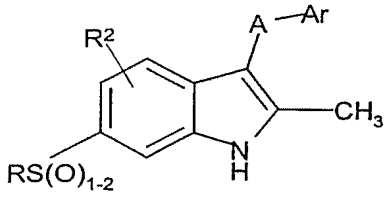
16. The use according to claim 13, wherein the disease is Alzheimer's.

17. A method for preparing a compound according to claim 1 wherein R^1 is methyl, R^3 is $-S(O)_{1-2}R^7$, R^4 is hydrogen and A is -S-, which comprises:

reacting a compound of general Formula



wherein R^2 is as defined in claim 1, and R is C_{1-6} alkyl,
with a compound of general Formula ArSH, to provide a compound of Formula (I):

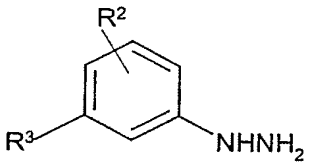


(I)

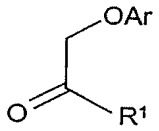
wherein R^2 and Ar are as defined in claim 1, A is S and R is C_{1-6} alkyl.

18. A method for preparing a compound according to claim 1 wherein R^4 is hydrogen and A is -O-, which comprises

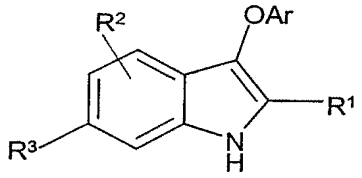
reacting a compound of general Formula



wherein R^2 and R^3 are as defined in Claim 1,
with a compound of general Formula



wherein R^1 and Ar are as defined in Claim 1,
to provide a compound of Formula (I):



(I)

wherein R^1, R^2, R^3, and Ar are as defined in Claim 1.

19. The invention as herein before described, particularly with reference to the new compounds, intermediates, uses and processes.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/10 C07D209/30 C07D209/36 A61K31/404 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 1 065 204 A (PFIZER) 3 January 2001 (2001-01-03) page 2, line 5 - line 40; claim 1	1-19
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2002	30/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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